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THE UNDERDEVELOPED SECRETORY ENDOMETRIUM

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MAMMALS have evolved highly specialized delicately balanced reproductive mechanisms which should assure them a high degree of reproductive efficiency. The dimensions of the problems of infertility and abortion in man, however, not to mention the heavy losses of ova and early embryos suffered by the proverbially fertile rabbit,<sup>1</sup> testify that this is not the case.

While biologists have been seeking the basic causes of embryonic mortality, clinicians have been obliged to treat infertile and aborting patients along largely empirical lines. As scientific facts have become established, and as diagnostic methods have improved, empirical treatments have to be scrutinized very critically in the light of new knowledge. The increased potency and the decreased cost of endocrine preparations have created the particular hazard that the use of hormones in an uncritical way may upset rather than regulate the delicately balanced reproductive process.

The purpose of this paper is to examine critically the problem of the underdeveloped secretory endometrium, particularly as to its incidence, the difficulties commonly encountered in its diagnosis, and the methods, and results, of its treatment. A clinical study has been carried out to see whether or not hormone therapy will significantly alter the course of endometrial development during the secretory phase of the cycle, and ovum transfers have been performed in the rat to determine to what extent an underdeveloped endometrium will interfere with implantation and development of the ovum.

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### Clinical Study

#### *Review of the Literature.—*

Underdevelopment of the secretory endometrium is referred to in nearly every serious study of the problems of habitual abortion and infertility. In papers in which particular attention has been given to the endometrium, a high incidence of abnormal secretory response is usually reported<sup>2-13</sup> but, when all etiological factors are considered, the endometrium is rarely found to be at fault.<sup>14-19</sup>

Table I lists the findings in twelve recent papers in which the endometrium was carefully studied. The true incidence of abnormal secretory endometrium cannot be deduced from this material, because the authors selected their patients in different ways and used various criteria for diagnosis.

TABLE I. THE INCIDENCE OF ABNORMAL SECRETORY RESPONSE IN THE ENDOMETRIUM OF INFERTILE AND HABITUALLY ABORTING PATIENTS

AUTHOR	NUMBER OF PATIENTS	PER CENT OF PATIENTS WITH ABNORMAL SECRETORY RESPONSE
Botella-Llusia <sup>2</sup>	300	10
Gandolfo-Herrera, Guixa, and Bearzi <sup>3</sup>	34	25
Gillam <sup>4</sup>	123	46
Glass and Lazarus <sup>5</sup>	50	66
Grant <sup>6</sup>	124	41
Hughes, Van Ness, and Lloyd <sup>7</sup>	324	58
Kantor and Harrel <sup>8</sup>	75	26
Kurzrok <sup>9</sup>	2667	33
Lyon <sup>10</sup>	18	32
Simmonds and Taymor <sup>11</sup>	100	7
Topkins <sup>12</sup>	259	12
Urgell-Roca and Ponjoan <sup>13</sup>	42	14

Gillam's<sup>4</sup> careful work exemplifies how the underdeveloped secretory endometrium may be diagnosed with only methods that are commonly available to clinicians. This author found that 57 of 123 selected patients had abnormal secretory endometria, although only 10.7 per cent of all his infertile patients showed this abnormality on a single biopsy. By interpolation, Gillam estimated that the true incidence of underdeveloped secretory endometria in his patients was 20 per cent.

The method that Gillam has used to date endometrial biopsies has been reasonably well standardized,<sup>20-26</sup> and quantitative aspects of the secretory response may be estimated objectively when this method is properly used. Unfortunately, however, by dating the average rather than the most advanced areas of endometrial response, by favoring one criterion, namely, minimal subnuclear vacuolation, over the many required for an unbiased evaluation, and particularly by taking clinical data into account in diagnosing the phase of the tissue, Gillam<sup>4</sup> has forfeited the objectivity of this method.

Two recent studies have shown that the apparent incidence of underdeveloped secretory endometrium is higher when biopsies are taken late in the cycle than when they are taken near the middle of the secretory phase. In the first of these studies,<sup>23</sup> a large number of endometrial biopsies was taken late in the secretory phase of the cycle, and 80 per cent of the endometria were found to be normal, that is, their histologic dates fell within 2 days of the date indicated by the shift in basal body temperature or by the onset of the succeeding menses. Only 5 per cent of the endometria showed advanced development, while 15 per cent seemed to be retarded. A test for linearity of regression, however,



showed that the number of retarded endometria in this series did not in fact differ significantly from the number of advanced endometria. Subsequently Kalant and associates<sup>27</sup> took 67 biopsies on or near the sixth postovulatory day of the cycle and found that 86.5 per cent were normal, 9.0 per cent were advanced, and only 4.5 per cent were retarded.

*Histochemistry.*—

Anatomists, pathologists, and clinicians have recently become intensely interested in the location and distribution of chemical substances in the endometrium. Wislocki and Dempsey<sup>28</sup> have shown that alkaline phosphatase is often located between the source of carbohydrate in the blood and the site of deposition of glycogen in mammalian endometria. This distribution supports the theory that by dephosphorylating hexosephosphate, alkaline phosphatase promotes glycogen condensation, and such activity would obviously be important in the storage of nutriment for the ovum and the embryo.

In the human being, alkaline phosphatase activity increases rapidly in the glandular epithelium during the late proliferative and early secretory phases of the cycle and falls rapidly after the sixth postovulatory day. Most of the activity of this enzyme is confined to the glandular epithelium and to the lumina of the glands. Atkinson and Engle<sup>29</sup> have shown that alkaline phosphatase is abundant when estrogen is dominant and is sparse when progesterone dominates, but that the quantity of this enzyme seems to vary widely from one endometrium to another. Valuable recent contributions on alkaline phosphatase have been made by Alamanni,<sup>30</sup> Arzac and Blanchet,<sup>31</sup> Burton,<sup>32</sup> Galbis-Pascual,<sup>33</sup> Hall,<sup>34</sup> Jones and co-workers,<sup>35</sup> and McKay and associates.<sup>36</sup>

Glycogen first appears at the basal poles of the glandular epithelial cells late in the proliferative phase of the cycle. After ovulation the glycogen migrates past the nuclei of the cells and into the lumina of the glands. After the eighth postovulatory day, glycogen appears in the cytoplasm of the stromal cells, where it is closely related to the predecidual reaction. Arronet and Latour<sup>37</sup> have shown that the total amount of chemically determinable glycogen in the human endometrium does not agree very closely with its histochemical determination. Chemical methods indicate a sharp peak of glycogen storage on the third and a sharp drop on the eighth postovulatory day. The endometria of 5 of 18 patients studied by these authors contained abnormal amounts of glycogen in otherwise normal secretory endometrium, but 3 of these 5 patients subsequently became pregnant. Hughes, Van Ness, and Lloyd<sup>7</sup> believed that glycogen deficiency is an important factor in sterility and in habitual abortion. Augustin,<sup>38</sup> Forbes and Heinz,<sup>39</sup> and Marinaccio and collaborators<sup>40</sup> have contributed significantly to our knowledge of endometrial glycogen.

Other interesting histochemical relationship in the endometrium have been elucidated by Dempsey and Wislocki,<sup>41</sup> Page and associates,<sup>42</sup> and McKay and co-workers,<sup>36</sup> but no clearly defined abnormality in endometrial histochemistry has as yet been related to the problems of infertility and habitual abortion.

*Hormone Therapy.*—

Whether a given case of underdeveloped secretory endometrium is caused by failure of the corpus luteum or is due to delayed endometrial response cannot be determined at present. Good results have been obtained by stimulating the ovary with gonadotrophins, however. Hamblen and Davis<sup>43</sup> reported that 18 per cent of infertile patients with immature progestational endometria became pregnant following equine and chorionic gonadotrophin therapy. Brown and Bradbury,<sup>44</sup> Segaloff, Sternberg, and Gaskill,<sup>45</sup> and others have shown that chorionic gonadotrophin will prolong the life of the human corpus luteum.

Fried and Rakoff<sup>46</sup> were able to rectify defects in the secretory endometrium with chorionic gonadotrophin and prolactin. R. Palmer<sup>47</sup> obtained 7 pregnancies in 19 patients with "troubles de receptivité" by administering chorionic gonadotrophin after ovulation. A. Palmer<sup>48</sup> gave chorionic gonadotrophin to prolong the short "hiphase" of the basal body temperature and, of 84 patients so afflicted, 53 became pregnant following therapy. Weir and associates<sup>49</sup> believed that they could effect the release of intrinsic pituitary gonadotrophin by administering small doses of estrogen before ovulation.

Many authors have reported pregnancies following postovulatory progesterone, or estrogen and progesterone therapy. Few of these authors, however, have used as much as the 50 mg. of progesterone in oil by daily injection and 1 mg. of diethylstilbestrol daily by mouth, which Bradbury, Long and Durham<sup>50</sup> have found to be minimum doses of these steroid hormones that will prolong the secretory phase of the cycle. Tyler<sup>51</sup> and others have successfully utilized a combination of steroid and gonadotrophic hormones.

#### *Materials and Methods.—*

Between September, 1954, and April, 1957, 72 patients who had been unable to conceive after a year of effort, who had no obvious cause for sterility, and who had recorded regular basal body temperature (BBT) curves, were given hormones, and endometrial biopsies were taken during the secretory phase of two menstrual cycles. Lack of data or of tissue excluded 12 patients from further study, but each of the remaining 60 patients were treated for 6 days, beginning as soon as possible after the shift in the BBT, and an endometrial biopsy was taken near the ninth postovulatory day.

Half of the patients were treated with hormones during the first cycle and were given oral or injected placebos in a later cycle. The other half were given the placebos first and the hormones later. Different hormones were given to 5 groups of patients, each group containing 12 women:

1. Progesterone was administered intramuscularly in oil, 100 mg. or more being injected every other day.
2. Estrogen was administered orally as 0.05 mg. ethinyl estradiol twice daily.
3. Chorionic gonadotrophin was given intramuscularly in doses of either 3,333 or 6,666 I.U. every other day, or 2,000 or 4,000 I.U. daily for 5 days.
- 4 and 5. Patients in the two remaining groups received the same doses of either progesterone and estrogen, or of progesterone, estrogen, and chorionic gonadotrophin given simultaneously.

The endometrium was fixed in 80 per cent alcohol at 4° C. for 24 hours and embedded in paraffin. The two biopsies from a given patient were sectioned and stained at the same time and in the same solutions. In addition to the routine hematoxylin and eosin, the sections were stained with Best's carmine for glycogen, and by the Gomori method for alkaline phosphatase. When 100 hematoxylin-stained biopsies had accumulated, they were arranged as unknowns in random order and were given histologic dates by the writer in accordance with previously standardized criteria.<sup>22</sup> The pairs of biopsies were then identified, and the effect of the hormone treatment was judged by comparing the endometrial histologic date with the BBT date or with the date of onset of the succeeding menses (MEN).

An actual case record will serve to illustrate how these calculations were carried out.

Mrs. M. J. was given oral placebos and solvent injections following the shift in the BBT as shown in Fig. 1. An endometrial biopsy taken on day 8 BBT was read histologically as day 7 endometrium, therefore the control cycle was scored  $7 - 8 = -1$  BBT.

After the next ovulation this patient was given progesterone, estrogen, and chorionic gonadotrophin, and a biopsy taken on day 7 was read day 9, so the treated cycle was scored  $9 - 7 = +2$  BBT. The score of the control cycle was then subtracted from the score of the treated cycle giving the *net change in endometrial date following hormone administration*, data based on BBT. In Mrs. M. J.'s case, hormone administration resulted in a  $2 - (-1) = 3$  day advancement of endometrial development. A similar system was used to obtain the net change in endometrial development when the onset of succeeding menses was used as the point of reference.

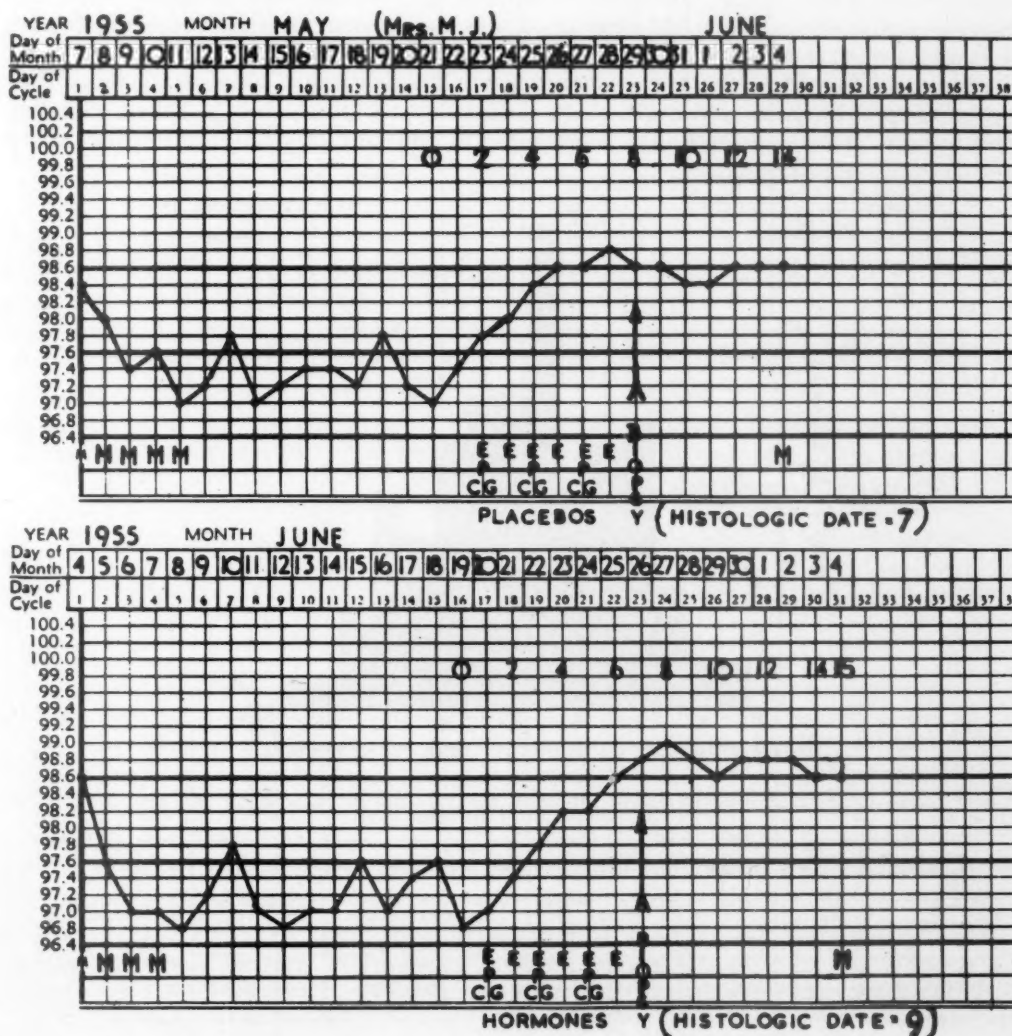


Fig. 1.—The basal body temperature record and the times of hormone administration, biopsy, and onset of menses in a control and in a treated cycle of a patient in this series.

### Results.—

Although the method of this clinical study called for biopsy on about the ninth day of the secretory phase, the exigencies of the moment required that some of the biopsies be taken both earlier and later in the cycle, as is shown in Fig. 2. Biopsies were in fact taken from 6 patients beyond the fourteenth postovulatory day according to the BBT, and even if all 6 biopsies had been



given the maximum possible histologic dates of 14 days, their minus scores would have indicated apparently retarded endometrial responses. Fortunately, these spuriously low scores were distributed in such a way that they did not in themselves significantly influence the results in any single treatment group.

Figs. 3 and 4 show the net advancement or retardation of endometrial development of each of the 12 patients following each of 5 kinds of hormone therapy. These data were found to be normally distributed, the chi-square goodness of fit for BBT being 7.43 with 4 degrees of freedom, and the chi square for MEN being 7.04 with 5 degrees of freedom; and homogeneous, the homogeneity of variance by Bartlett's test chi square for BBT being 2.16 with 4 degrees of freedom, and the chi square for MEN being 4.91 with 4 degrees of freedom. Therefore, the t-test, using a variance estimate obtained from scores on all 5 treatments, was applied to determine whether any of these hormone treatments was followed by a significant advancement or retardation in endometrial development.

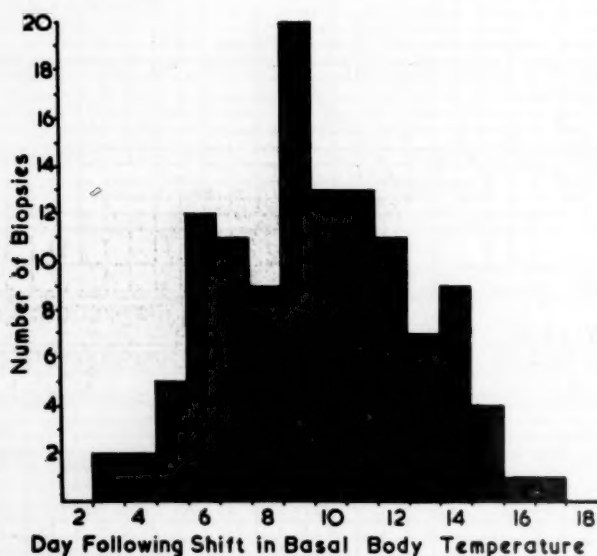


Fig. 2.—The number of biopsies taken on each day of the secretory phase of the cycle in 60 patients (120 biopsies).

TABLE II. THE MEANS, *t* VALUES, AND LEVELS OF SIGNIFICANCE OF THE DATA GIVEN IN FIGS. 2 AND 3

HORMONE ADMINISTERED	NO. OF PATIENTS	BASAL BODY TEMPERATURE			SUCCEEDING MENSES		
		MEAN EFFECT (DAYS)	<i>t</i> WITH 55° OF FREEDOM	LEVEL OF SIGNIFI- CANCE	MEAN EFFECT (DAYS)	<i>t</i> WITH 55° OF FREEDOM	LEVEL OF SIGNIFI- CANCE
Progesterone	12	0.00	0.00		-0.25	0.31	
Estrogen	12	-2.17	3.69	0.001	-1.58	1.99	
Progesterone and estrogen	12	-0.75	1.27		-1.33	1.68	
Chorionic gonadotrophin	12	+1.17	1.99		+1.75	2.20	0.05
Progesterone, estro- gen, and chorionic gonadotrophin	12	+0.50	0.85		+0.75	0.94	
Standard error		0.59			0.79		



Table II gives the means, t values, and the levels of any significant effects for each treatment. Estrogen significantly decreased endometrial development when the shift in BBT was used as a reference point, and chorionic gonadotrophin significantly advanced the endometrial development when the succeeding menses was used as the reference point. The standard error of the 5 means was significantly lower when the BBT was used than when the MEN was used for reference.

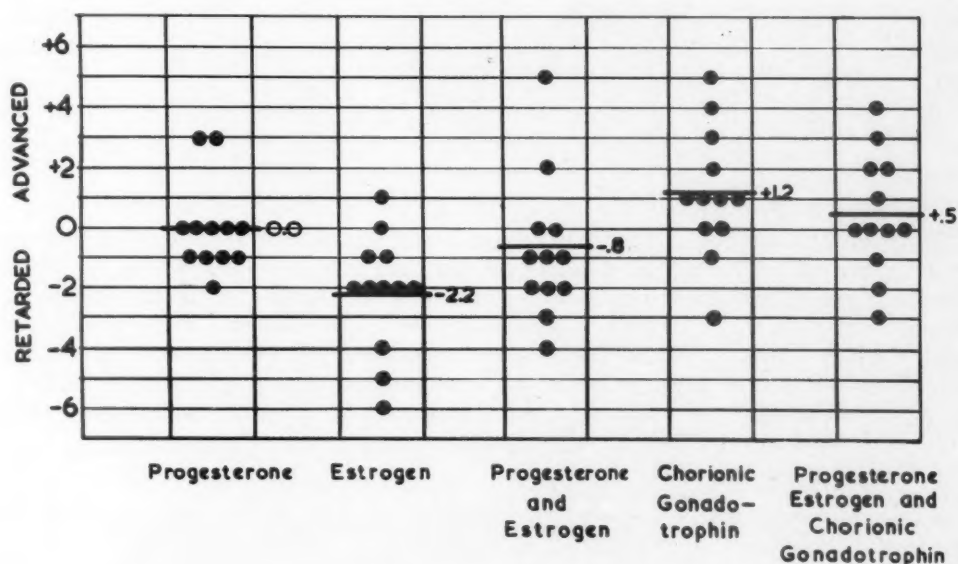


Fig. 3.—The net change in endometrial date following hormone administration. Data based on the shift in basal body temperature. Unit is one day.

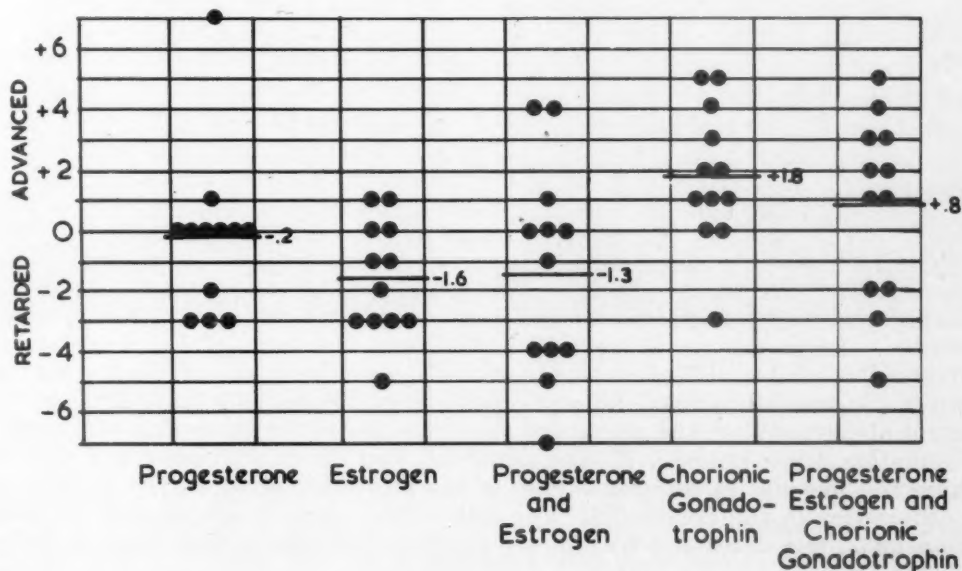


Fig. 4.—The net change in endometrial date following hormone administration. Data based on the time of onset of the menses that followed the biopsy.

The effect of giving estrogen together with progesterone was not significantly different from the total of the effects of estrogen and progesterone given separately, and the effect of giving estrogen, progesterone, and chorionic gonadotrophin together was not significantly different from the total of the effects of giving estrogen and progesterone together and chorionic gonadotrophin separately. Since there was no evidence in the data that any of the hormones used interacted with each other to a significant degree, the over-all effect of each hormone was summated for all of the groups in which that particular hormone was given. These summated effects are given in Table III. This more efficient utilization of the data has improved the levels of significance of the retarding effect of estrogen and the advancing effect of chorionic gonadotrophin.

At the time of writing, 10 months have elapsed since the last patient was treated. Twenty-six patients have become pregnant, and 4 of these have aborted. Conditions sufficient to explain the infertility have been found in 9 patients, but the cause of the infertility remains obscure in 46 cases.

Both the treated and the control endometrial biopsies showed a retardation of more than 2 days in 4 patients, and an advancement of more than 2 days in 2 patients, when only one reference point (BBT or MEN) was considered. Only one of these 6 patients showed an abnormal pattern in both biopsies when both BBT and MEN were considered (her endometrium was 3 days advanced), and only 3 patients were abnormal in 3 of the 4 possible scores utilizing BBT and MEN in both biopsies. Three of these last 4 mentioned patients have had a normal pregnancy.

TABLE III. THE MEANS, *t* VALUES, AND LEVELS OF SIGNIFICANCE OF THE OVER-ALL EFFECT OF A GIVEN HORMONE ASSUMING NO INTERACTION BETWEEN THE HORMONES ADMINISTERED TOGETHER

HORMONE ADMINISTERED	BASAL BODY TEMPERATURE			SUCCEEDING MENSES		
	MEAN EFFECT (DAYS)	<i>t</i> WITH 55° OF FREEDOM	LEVEL OF SIGNIFICANCE	MEAN EFFECT (DAYS)	<i>t</i> WITH 55° OF FREEDOM	LEVEL OF SIGNIFICANCE
Progesterone	+0.47	<1.0		-0.08	<1.0	
Estrogen	-1.69	3.53	0.001	-1.42	2.18	0.05
Chorionic gonadotrophin	+1.19	2.49	0.05	+1.86	2.87	0.01
Standard error	0.48			0.65		

**Histochemistry:** In the last 4 treatment groups, the biopsies were stained histochemically and were read in pairs as unknowns. For example, the two biopsies of a given patient were compared for the amount of glycogen contained in the glandular epithelium, and a plus score was given to the biopsy showing the most stain. If no difference could be seen, a zero score was recorded. Later the slides were identified, and the signs of the scores were converted, so that a plus score would indicate a predominance of histochemical stain in the treated biopsy, and a minus score would indicate more stain in the control biopsy. When the scores for the activities of glycogen and of alkaline phosphatase were studied, it was apparent that more variation was due to taking the biopsies at different times of the secretory phase of the cycle than to differences in the treatment. For this reason, only those pairs of biopsies whose histologic dates fell within two days of each other have been included in Table IV.

Hormone treatment had no significant effect on glycogen activity in the glandular epithelium or in the stroma of these 29 patients. The fact that 3 of

6 patients treated with estrogen and progesterone showed decreased glycogen activity in the stroma is probably a chance effect.

Alkaline phosphatase activity was increased by estrogen in 5 of 7 patients, and the endometrium of the remaining 2 had advanced to the twelfth and fourteenth postovulatory days, at which time alkaline phosphatase activity is always at a minimum. Figs. 5 and 6 show the lightly stained glandular

Fig. 5.

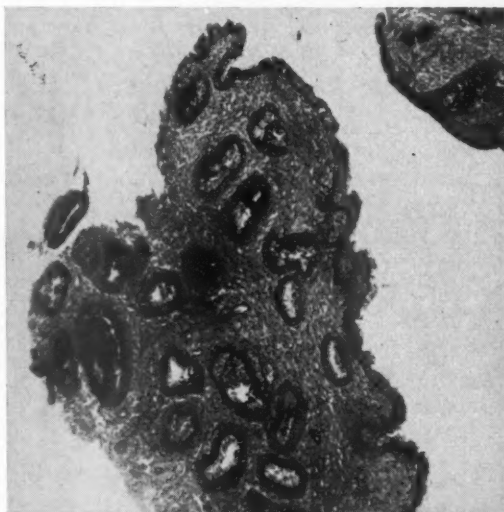


Fig. 6

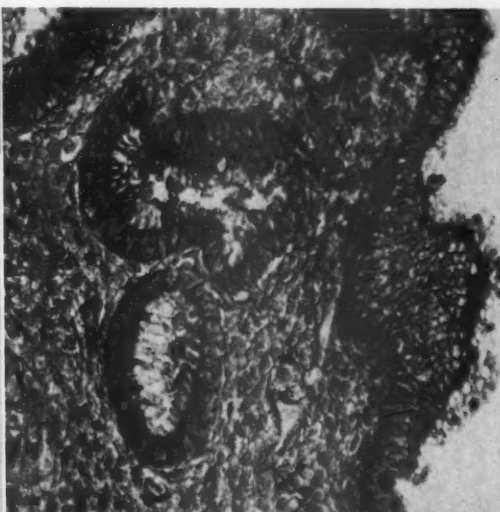


Fig. 7.

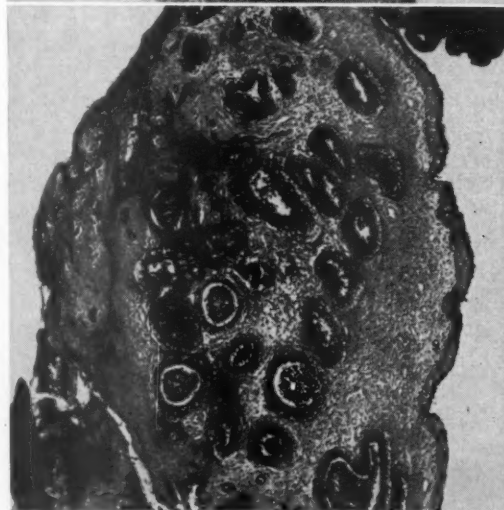


Fig. 8

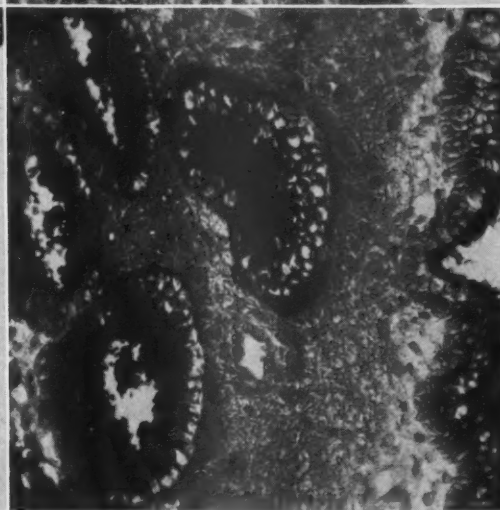


Fig. 5.—Endometrial biopsy No. 56-1206 taken from a patient in this series, on the seventh day following the shift in basal body temperature, in a cycle in which placebos had been administered between the second and the seventh "postovulatory" days. A histologic date of 7 day endometrium was independently assigned to this entire specimen. This section was stained in the same solutions as biopsy No. 56-1304 shown in Fig. 7 below by the Gomori technique for alkaline phosphatase, the activity of which is seen to be confined to the lumina of a few endometrial glands. ( $\times 100$ ; reduced  $\frac{3}{11}$ .)

Fig. 6.—A high-power field from Fig. 5 showing the absence of activity of alkaline phosphatase in the glandular epithelium. ( $\times 940$ ; reduced  $\frac{3}{11}$ .)

Fig. 7.—Endometrial biopsy No. 56-1304 taken from the same patient as in Figs. 5 and 6, on the eighth day following the shift in basal body temperature, in a cycle in which ethinyl estradiol 0.05 mg. had been administered twice daily between the second and the seventh "postovulatory" days. A histologic date of 6 day endometrium was independently assigned to this entire specimen. The alkaline phosphatase activity is abundant in all the endometrial glands. ( $\times 100$ ; reduced  $\frac{3}{11}$ .)

Fig. 8.—A high-power field from Fig. 7 showing intense alkaline phosphatase activity in the glandular epithelium. ( $\times 940$ ; reduced  $\frac{3}{11}$ .)

TABLE IV. THE NET INCREASE (+) OR DECREASE (-) IN THE ACTIVITY OF GLYCOGEN AND OF ALKALINE PHOSPHATASE FOLLOWING TREATMENT WITH VARIOUS HORMONES

ESTROGEN						ESTROGEN AND PROGESTERONE						CHORIONIC GONADOTROPHIN						ESTROGEN, PROGESTERONE, AND CHORIONIC GONADOTROPHIN					
GLYCOGEN			ALKALINE PHOSPHATASE			GLYCOGEN			ALKALINE PHOSPHATASE			GLYCOGEN			ALKALINE PHOSPHATASE			GLYCOGEN			ALKALINE PHOSPHATASE		
EPITHE- LIUM	STROMA		EPITHE- LIUM	LUMEN		EPITHE- LIUM	STROMA		EPITHE- LIUM	LUMEN		EPITHE- LIUM	STROMA		EPITHE- LIUM	LUMEN		EPITHE- LIUM	STROMA		EPITHE- LIUM	LUMEN	
+	0	+	0	-	0	0	0	0	+	0	+	+	+	+	+	0	+	+	+	+	+	-	+
-	0	0	0	0	0	0	-	0	0	0	0	-	0	0	0	0	0	+	+	0	-	0	0
+	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	+	+	0	0	0	0	0	+	+	+	0	0	0	0	0	0	0	0	0	+	0	0
-	0	+	+	+	0	0	-	-	-	-	-	+	+	+	0	0	0	0	0	0	0	0	0
0	0	+	+	+	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0
0	0	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	-	+	0	+	0	0



epithelium and low degree of activity in the lumen characteristic of the endometrium of the seventh postovulatory day. Following estrogen therapy, the alkaline phosphatase activity was increased abnormally, as is shown in Figs. 7 and 8.

### Animal Experiments

The ova of some mammalian species can develop normally in the absence of nutritional factors supplied by the uterus. Burdick and associates<sup>52</sup> found that mouse ova locked in the oviduct with estrogen therapy grew into normal late blastocysts. Alden<sup>53, 54</sup> has shown that rat ova will grow normally in the ligated oviduct, and in the nonligated oviduct following bilateral ovariectomy. Similar findings have been reported for the sheep<sup>55</sup> and rabbit.<sup>56</sup>

Conditions similar to those encountered by ova in underdeveloped and in overdeveloped endometrial cavities can be simulated by transferring ova from the oviducts into the uterus of experimental animals at various phases of the estrus cycle and early pregnancy. Chang<sup>57</sup> transferred fertilized ova into the oviducts or uteri of pseudopregnant rabbits, and reported that when the endometria were more than 2 days advanced or retarded relative to the development of the ova, implantation did not occur. McLaren and Michie<sup>58</sup> found that more mouse ova survived when they were transferred to underdeveloped uteri than when they were transferred to uteri at the same stage of development as the ova, but when the uteri were as little as one day overdeveloped in relation to the ova, none of the ova survived.

#### *Materials and Methods.—*

Twenty-two homozygous, black-hooded female rats were mated with black males and were killed on the first day that a vaginal plug was found. The oviducts were excised and washed through with filtered tissue culture medium in which mouse sarcoma cells had been growing for several days. If the recovered ova were still enmeshed in the cumulus mass, they were taken up into a micropipette and were injected at laparotomy through the bursal foramina into the ovarian bursae of albino recipient rats. If the ova were free of granulosa, they were injected directly into the fimbriated ends of the recipient's oviducts in 0.001 ml. of medium.

The vaginal cytology technique was used to establish the estrus cycle of the recipient rats, and an average of 5 ova (range 3-11) were transferred to both oviducts of one recipient 2 days before estrus, of 3 recipients one day before estrus, and of 6 recipients on the day of estrus (day 0 of the estrus cycle and pregnancy). These 10 albino recipient rats were mated with albino males, and vaginal plugs were noted the next day. One-day ova were transferred to the oviducts of 4 recipients on the first, of 6 recipients on the second, and of 2 recipients on the third day of pregnancy. Preliminary experiments had shown that ova transferred on any of these days of the cycle or pregnancy entered the uterus of the recipient animal 4 days later.

Additional ova were recovered from the uteri of 11 more black donors on the fifth day of pregnancy, and an average of 5 of these 5 day ova were injected at laparotomy through the wall of the uterus into the endometrial cavities of both uterine horns of 2 albino recipients on the third, 3 on the fourth, 4 on the fifth, and 2 on the sixth day of pregnancy.

The 33 albino recipient rats were operated upon on the eighteenth day of pregnancy, at which time the transferred ova that had implanted successfully had developed into embryos with black iris pigment, which clearly distinguished them from the nonpigmented control embryos occupying the same uterine horn.

### Results.—

Neither transferred nor control embryos were found in the uterine horns of 5 recipient rats following 66 transfers of ova. Fig. 9 shows the results of the remaining 61 transfers. When 1 day ova were transferred synchronously to the oviducts of recipients on the first day after estrus, 5 of 7 transfers succeeded, and 21 of 42 ova survived. When 1 day ova were transferred to recipients on the day of estrus, 6 of 11 transfers succeeded, and 14 of 51 ova survived, but when 1 day ova were transferred to recipients on the second day after estrus, only 2 of 12 transfers succeeded and only 2 of 67 ova survived. When 5 day ova were transferred to the uterus the results were very similar.

Since the 1 day ova took 4 days to travel through the oviducts and were 5 day ova when they entered the uterus, the results of the transfers of all 304 ova can be summated in terms of 5 day ova entering the uterus on various days of pregnancy, as has been done in Fig. 10. When ova were transferred so that their stage of development was synchronized with that of the recipient animal, half of the ova survived. When the recipient's endometrium was one day retarded in relation to the development of the transferred ova, one third of the ova survived, but when the recipient's endometrium was one day advanced, very few ova survived.

### Comment

Only selected patients can be studied carefully enough to establish the difficult diagnosis of underdevelopment of the secretory endometrium. Unfortunately this need to select patients prevents the accomplishment of a properly controlled study, such as one that would compare the endometrial responses of infertile and aborting patients with those of normal women, to determine the true incidence of this condition. By carefully standardizing diagnostic techniques, however, one should be able to select from a population of patients with reproductive problems those few whose postovulatory endometrial responses are definitely and consistently abnormal.

The first difficulty encountered in standardizing diagnostic techniques is that there is no reliable method for determining temporal or endocrinological reference points from which to measure endometrial variability, in other words, we do not know when ovulation occurs or how much steroid hormone is being produced from day to day. The onset of menses is widely accepted as a reference point because it is supposed to indicate a sudden drop in steroid hormone production occurring on about the fourteenth day of the life of the corpus luteum. Markee<sup>59</sup> has shown, however, that in the monkey the true end point of steroid production is signalized by endometrial ischemia, and that hemorrhage may occur from minutes to days later. The shift in basal body temperature is related to a sudden alteration in steroid metabolism, but Greulich,<sup>60</sup> Buxton and Engle,<sup>61</sup> and others have shown that the time of this shift does not always coincide exactly with the time of ovulation. Although this study showed that the endometrial response was correlated better with the temperature shift than with the onset of menses, both of these points are subject to occasional wide errors, and common sense suggests that both of these reference points should be used rather than an attempt made to select the better of the two.

A second problem in standardizing diagnostic technique is the selection of the time in the secretory phase of the cycle in which biopsies should be performed. Those who favor taking biopsies at the end of the secretory phase argue that the stromal predecidual reaction is an important criterion of secretory response. The ovum implants before the predecidua appears, however, so that the importance of the predecidua, at least as a nutriment for the ovum,

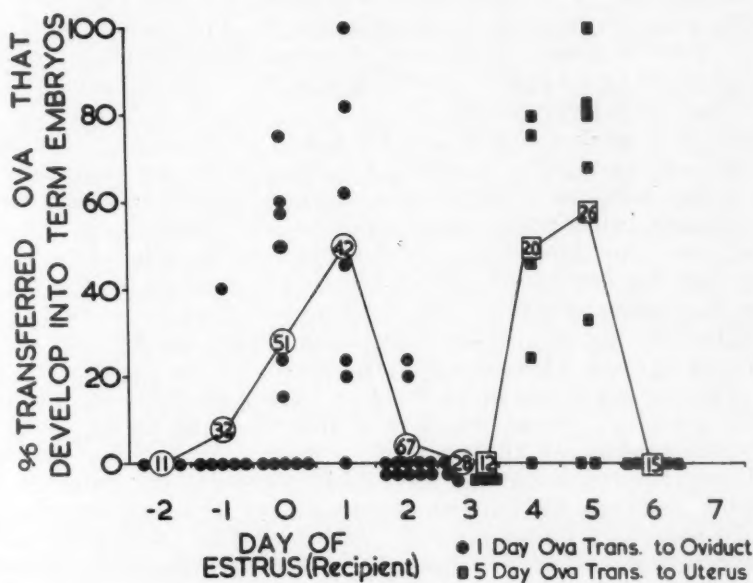


Fig. 9.—The per cent of 1 day and of 5 day rat ova that developed into term embryos when transferred into the oviducts and into the uterine horns of recipient rats on various days of the estrus cycle and early pregnancy. The enclosed figures indicate the total number of ova transferred on a given day.

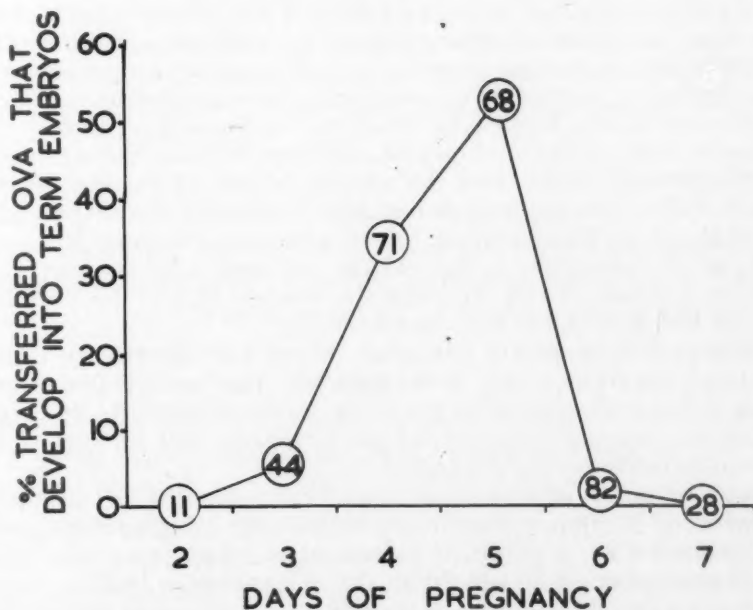


Fig. 10.—The data of Fig. 9 summated in terms of the percentage of 5 day ova that developed into term embryos when they first entered the endometrial cavity on a given day of pregnancy.



is doubtful. The argument that biopsy on the first sign of menstrual bleeding will avoid interrupting a pregnancy is weakened by the fact that uterine hemorrhage is not uncommon in early pregnancy. The chance of destroying an implanting ovum is small, as witness the considerable number of patients who become pregnant in a biopsied cycle, and by the extreme rarity of finding young trophoblast in biopsy material.

When most of a group of biopsies are taken at the end of the secretory phase, any and all histologic variations must appear to represent underdevelopment simply because there are no criteria by which to assess variations beyond the optimum in secretory development. For example, in the endometrial dating system, the latest stage of development is called day 14, and no variations beyond this are dated. If all biopsies are taken on the fourteenth postovulatory day many would be dated 12 and 13, but none could be dated 15 and 16. This difficulty is not peculiar to the dating system, but is common to any measuring system when most of the readings are taken near the end of the scale. This problem can be avoided by taking biopsies at random times throughout the secretory phase, which is a difficult thing to do, or by taking biopsies near the middle of the secretory phase. Variations will then be more normally distributed about the mean, and there will be apparent cases of overdevelopment as well as underdevelopment of the endometrium. The "overdeveloped secretory endometrium" will doubtless provide a new worry for those who are now concerned because of the artificial importance given the underdeveloped secretory endometrium by the biopsy times now commonly employed.

A third problem in standardizing diagnosis is the establishment of objective histologic criteria for reading endometrial biopsies. Since the ovum implants on the surface of the fundal endometrium, the microscopist should give most of his attention to the fundal surface layers in the endometrial biopsy. It is harder to reach the fundal endometrium with the biopsy curette, however, than it is to reach the lower uterine segment endometrium, so the latter frequently predominates in biopsy material. It is easy to gouge out with the curette a neat tunnel of unresponsive basal endometrium and leave the desired stratum compactum intact, especially when the endometrium is very deep at the end of the secretory phase of the cycle. Biopsy fragments are haphazardly arranged in the paraffin block, and the various planes of section represented on the finished slide give an impression quite different from that of a sectioned block of the same endometrium, where attention is almost automatically focused on the more responsive areas. These are particular reasons why only the best-developed areas of the endometrial biopsy should be dated rather than the average of a number of microscopic fields.

Which histologic criteria are the most useful for objectively evaluating endometrial responsiveness, and how uniform the endometrial secretory response is have been discussed in previous publications.<sup>22-26</sup> It is obvious that objectivity in judging endometrial development will be lost if clinical data are allowed to influence the diagnosis.

The proper evaluation of treatment is an even more difficult problem than the establishment of a proper diagnostic technique. Evaluating the probability that pregnancies are a result of treatment is a hopeless task. Evidence for therapeutic success must be sought in the endometrium itself.

It was surprising to find that what seemed at the outset of this study to be such drastic hormone therapy had so little effect on the endometrium. The retarding effect of estrogen though slight was definite, as was demonstrated both histologically and histochemically. Histologic evidence in this study suggested that chorionic gonadotrophin advanced secretory endometrial development. This effect was not caused by prolonging the secretory phase of the



cycle, and the advancement was not enhanced by the addition of steroid hormones. Nothing in the data suggests that a combination of progesterone and chorionic gonadotrophin would have advanced the endometrium more than did chorionic gonadotrophin alone.

The facts that some mammalian ova are able to develop normally within the oviduct during a stage when they should normally be in the uterus, that the ova of many species survive long periods of delayed implantation in a type of underdeveloped endometrium, and particularly that transferred ova survive better in an underdeveloped than in an overdeveloped endometrium suggest that perhaps the hazards of the underdeveloped secretory endometrium have been exaggerated.

An association of the ideas that overdeveloped endometrium may be detrimental and that estrogen will depress secretory response suggests that post-ovulatory estrogen therapy might be tried on infertile and aborting patients. Estrogen has many other powerful actions on the reproductive system, however, such as that of locking ova in the oviduct,<sup>54</sup> the net result of which would be difficult to assess.

### Conclusions

The diagnosis of secretory underdevelopment of the endometrium is much more difficult than has been generally appreciated. Biopsies should be taken from the surface layers of the fundal endometrium at about the middle of the secretory phase of at least 2 menstrual cycles, and both the basal temperature shift and the onset of succeeding menses should be used as points of reference to time the length of the secretory phase. The most developed areas of the endometrium should be dated, with strict objectivity, by carefully standardized histologic criteria. When the two histologic dates are compared with the corresponding temperature shift and menstrual dates, at least three, and preferably all four, of the resulting endometrial response dates should be more than 2 days retarded before the diagnosis of underdeveloped secretory endometrium is entertained.

Present histochemical methods are not likely to reveal secretory deficiencies that are not disclosed by histologic examination alone.

The significance of underdeveloped secretory endometrium has possibly been overrated. The ova of several species of animals are known to survive deficient environments in the oviduct, or in the uterus when the endometrium is retarded, but ova are rapidly destroyed when they are transferred into an overdeveloped endometrial environment.

The effectiveness of hormone therapy should be judged on the basis of changes noted in endometrial development, rather than on how many patients subsequently conceive or maintain a normal pregnancy.

The histologic and histochemical responses of secretory endometrium can be retarded by postovulatory estrogen therapy. Chorionic gonadotrophin may advance the histologic response slightly, but progesterone, as given in this study, has no effect on endometrial development.

There is little evidence in this study that rather large doses of hormones administered between the times of ovulation and implantation will markedly upset the balance of the reproductive system. However, until the incidence of underdevelopment of the secretory endometrium has been more carefully

determined, until its significance is better understood, and particularly until it can be shown that the rare malfunctioning endometrium can in fact respond to extrinsically administered hormones, the endocrine treatment of infertile and aborting patients for this condition must be considered to be still empirical rather than rational therapy.

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## IMMUNOLOGY, FERTILITY, AND INFERTILITY: A HISTORICAL SURVEY\*

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SINCE the time of Malthus<sup>1</sup> the specter of overpopulation outracing food supply has been alternatively derided or underscored. Most recently, men of serious thought<sup>2, 3</sup> have turned the light of deep concern upon this disquieting apparition and have concluded that populations must be controlled and soon, for even the most ingenious methods projected for increasing the world's food supply will not long delay the ultimate crisis. If these men are correct, then something should be done immediately for it may be too late to wait and see, since, at the current rate of population increase (47 million per year), the world's population will have doubled within 40 years.<sup>4</sup>

The problems associated with the control of populations are many and it does no good to recount them. The core of the matter is that, as yet, no effective and reliable method is available for inducing sterility (temporary or permanent) in both males and females which will meet with the approval of the greatest numbers of people, although recent developments in steroid congeners seem promising.

As the varieties of measures that might be undertaken were considered, the possibility of employing immunological procedures to control fertility seemed worthy of exploration because we had been wondering, at the time, whether certain inexplicable cases of infertility might be due to an immune response(s). We, therefore, set out to examine the literature to determine whether an immunological approach to the control of fertility had been investigated. As the survey of the literature progressed, a fascinating picture unfolded. It is the purpose of this review to reveal the story in a historical manner, and the hope is to stimulate intensive experimentation and clinical investigation in this broad area of the control of infertility and fertility by immunological means for, as will be seen, fulfillment or rejection of promise by way of incontrovertible evidence is yet to be secured. A complete recapitulation of all studies plus a critique of each would not be possible outside a lengthy tome. Therefore, emphasis will be placed on what are thought to be key references and tantalizing results with an attempt to give equal attention to negative and to positive reports.

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Finding the first individual who suggested that fertility or infertility might be integrated with what we know today as an immune response seems impossible. Certainly, though, anyone with this theme in mind when reading Darwin's *The Descent of Man*<sup>5</sup> could easily seize upon the number of references to the profligacy of women in connection with reduced fertility as suggestive. For example, one such reference is, "No doubt the profligacy of the women may in part account for their small fertility." If we are to lean towards an immunologic interpretation of Darwin's statement, we could infer that repeated exposure to antigenic material, sperm, had induced infertility. But it would have to be demonstrated that sperm are antigenic.

Almost simultaneously this demonstration was made by Landsteiner,<sup>6</sup> Metchnikoff,<sup>7</sup> and Metalnikov,<sup>8</sup> who observed that injections of sperm or testicular extracts into experimental animals resulted in antibody formation. Immediately, reports appeared which could be used to support the rationale of inducing sterility by immune methods. von Moxter<sup>9</sup> injected ram sperm into rabbits and obtained antisera which were spermicidal to rat sperm. de Leslie<sup>10</sup> noted that male mice became sterile for short intervals (16 to 20 days) after receiving injections of antisperm serum obtained in guinea pigs. Farnum<sup>11</sup> injected female rabbits intraperitoneally five to eight times with semen or testicular material of dog, bull, or man at intervals of 2 to 6 days. He concluded that the sera of the treated animals contained precipitins which were specific for each antigen, since precipitates were obtained for each antigen selectively when titrated against the antisera. He also recorded that the amniotic fluid of one of the rabbits gave the same reactions as her serum.

Pfeiffer<sup>12</sup> injected rabbits with dried and powdered bull sperm extracts. The resulting antiserum reacted strongly with semen solutions and testis extracts and negligibly, if at all, with extracts of other bovine organs. It was possible also to absorb out all other precipitins in mixtures of antiorgan antisera, so that only those specific for semen remained. Strube<sup>13</sup> also obtained precipitins by injecting rabbits with human semen and testicular extracts. Ricketts<sup>14</sup> has recorded that castrated animals can be immunized successfully with sperm and, therefore, "amboceptor" production by the homologous organ is not essential. Moreover, he mentioned that immunization with the "plasma of ova" evoked the production of antisperm toxins. Taylor<sup>15</sup> concluded that the ether-soluble fraction of salmon sperm did not induce antibody formation in rabbits, but that injections of whole sperm resulted in an antiserum which was cytotoxic for salmon sperm.

In 1911, Savini<sup>16</sup> attempted to induce sterility in female rabbits and guinea pigs with sperm injections. He injected 57 rabbits five to six times at weekly intervals subcutaneously or intraperitoneally with sperm and one week later exposed them for 10 to 15 days to males. No young were obtained from this exposure, but many fertile matings resulted from subsequent copulations. Kohlbrugge<sup>17</sup> claimed that, during copulation in rats, mice, bats, rabbits, and fowl, sperm penetrated the epithelial lining of the female reproductive structures and were absorbed there. He illustrated such an instance in the oviduct of a hen by means of a diagram showing sperm in the connective tissue layer. Walstein and Ekler<sup>18</sup> obtained an Abderhalden reaction for testicular protein after coitus in rabbits. The authors speculated as to what might have happened to the millions of sperm liberated into the female tract during copulation and concluded that the sperm were reabsorbed during residence in the uterus. Metalnikov and Strelnikov<sup>19</sup> placed sperm and testicular grafts with and without enclosure in collodion sacs in body tissues and recorded antibody production.

It was during these years that marine forms were used extensively to reveal the presence of an agglutinin in sea water in which *Arbacia* or *Nereis*

eggs were kept. From such studies Lillie's<sup>20</sup> theory of the phenomenon of agglutination was evolved and was based upon Ehrlich's side-chain theory.<sup>21</sup> The identity of the agglutinating substance and fertilizin was also advanced in theory by Lillie. Loeb,<sup>21</sup> however, questioned Lillie's findings and theories. (It is not the purpose of this review to consider the immunological aspects of the fertility or infertility of marine forms. Therefore, it is sufficient to note that this subject has been covered in the extensive work by Tyler and his colleagues.<sup>22</sup>)

Venema<sup>23</sup> cited experiments in which sterility resulted in female rabbits that were injected with testis. Dittler<sup>24</sup> injected female rabbits with sperm and 1 to 8 days after two injections of 2.5 ml. of sperm suspension given 4 days apart, sterility of short duration (weeks) was induced. The injection of large amounts of human semen was without effect, and Dittler, therefore, proposed that sterilization required the use of homologous material.

By the year 1921 the cumulative evidence was so appealing as to motivate an editorial in *The Journal of the American Medical Association*<sup>25</sup> asking, "If spermatozoa invade the female tissues and cause formation of specific antibodies which are capable of preventing fertilization, may not such a process participate in the problem of sterility? May not the traditional sterility of the prostitute depend sometimes on such a process. . . ." "May not such spermatoxic substances so modify the sperm or the fertilized egg as to lead to abnormalities of importance in teratology." These questions and possibilities were not to be denied by subsequent speculation and experimentation. Mayer<sup>26</sup> postulated that sex intemperance in women could lead to premature rupture of ovarian follicles and, thus, effect sterility. He speculated that during sexual abstinence, however, fecundity could return and cited evidence that during World War I abstinence facilitated postwar pregnancies in previously infertile matings. Vogt<sup>27</sup> also theorized that women might become sterile following frequent sexual indulgences. He was impressed that couples who failed to conceive had successful matings after periods of separation or abstinence. Moreover, he claimed that among animals the first copulation was often followed by pregnancy but that subsequent ones were not and invoked spermatoxins to explain the difference. It is impossible to evaluate such reports, obviously, yet even today proponents of such tenets are still to be found. One would think that animal experimentation studies should have provided conclusive evidence.

Guyer<sup>28</sup> prepared antisperm sera by injecting fowl repeatedly with rabbit sperm and found such sera not only toxic to rabbit and guinea pig sperm in vitro but also, when injected on five occasions intravenously at 4 to 5 week intervals into male rabbits, inducive to partial or complete sterility. Three rabbits were employed; in one the sterility was partial or temporary; in another, it was complete without evidence of testicular injury; in a third, marked degenerative changes were found in the testicles. McCartney<sup>29</sup> injected rat or human sperm or testis extract into female rats and observed that sterility of 2 to 22 weeks' duration was induced and that after resumption of reproductivity fewer offspring were littered. Upon injection of pregnant rats with sperm, 5 out of 13 animals aborted. Serologic examinations implied that the infertility was due to the presence of spermatoxins in the vaginal and uterine secretions, since these fluids immobilized and agglutinated sperm. Interference with the estrus cycle was ruled out. Upon injection of sperm into male rats, at least temporary atrophy of the testes was noted. The subcutaneous injection of rooster sperm into egg-laying hens did not influence the rate of egg production, but the eggs laid during the next 12 to 67 days were infertile. Chicken liver extract had no effect. Hektoen and Manly<sup>30</sup> injected human semen and fluids as well as extracts of human sperm in addition to swine, bovine, and equine seminal fluids

into rabbits and observed species and semen-specific precipitins. Kennedy<sup>31</sup> reported that: (a) both male and female guinea pigs could be sterilized by injections of guinea pig sperm; (b) the sperm-immobilizing capacity of the antibody serum was more potent in the sensitized male than it was in the immunized female; (c) degenerative changes occurred in the testicles of some of the injected males; (d) autologous injections were most effective in inducing sterility in the male. Oslund<sup>32</sup> injected male rats, guinea pigs, and rabbits with homologous sperm and found a variable degree of degeneration of the testes in 3 rats and none in 2 rabbits used. In the case of the guinea pig, the situation is unclear because Oslund's statement is confused: "In each of 4 experiments there was full spermatogenesis and the testes appeared normal. These animals had been used for bleeding purposes before these experiments were undertaken and control testes were also degenerated." Similarly, Oslund's finding that no infertility was induced in 6 female rats after injections of sperm must be viewed cautiously because of his statement that 3 rats mated successfully and 3 did not. He also stated that while sperm injections into female rats did not prevent or delay pregnancy, "it has caused abortion." No data were supplied.

Pommerenke<sup>33</sup> made the following observations: (1) the serum as well as the vaginal secretions of female rabbits injected with rabbit sperm or testicular extract were toxic for rabbit sperm; (2) after intravenous injections of rabbit sperm or testis into female rabbits, the longevity of sperm deposited in the genital tract during mating was greatly decreased; (3) infertility for 6 to 25 weeks was induced following repeated injection of sperm or testis in the female rabbit and injections of salivary gland or ejaculates of vasectomized males had no effect; (4) sterility caused by sperm or testis injections was not due to an effect on the ovulatory mechanism but if such materials were given during pregnancy, abortion or resorption of fetuses occurred in some cases; (5) apparently cross-reactions occurred between rabbit and rat sperm because the serum of rabbits injected with rabbit sperm was toxic for rat sperm, and the serum of rabbits which received rat sperm was toxic for rabbit sperm; (6) repeated intravaginal injections of rabbit sperm into female rabbits led to detectable antigenicity in the serum as well as in the vaginal secretions of these rabbits, but Pommerenke was unable to obtain conclusive evidence that sterility could be induced by intravaginal injections of sperm.

In 1926, Landsteiner and Levine<sup>34</sup> demonstrated that sperm cells of humans of appropriate blood type absorbed specifically and almost completely immune antibodies (from rabbits) to the A and B antigens of human erythrocytes. Jarcho's<sup>35</sup> paper was intriguing from several aspects: (1) He mentioned (without providing a reference) that "Van der Dyck states that the blood serum of sterile women in whom no other cause of sterility can be found always belongs to the agglutinating group." (2) He injected female rabbits with formalin-killed sperm of sheep or guinea pig and recorded that the animals were sterile for longer than 7 months. (3) He was unable to demonstrate any consistent difference between the sera of immunized and control does, nor was he able to find evidence of spermatotoxic substances in the vaginal secretions of the injected animals.

Quick<sup>36</sup> injected homologous sperm or testicular homogenate into rats and interpreted the degenerative changes he found in the testicles as due to cyst formation in the epididymides and/or displacement of the testes. Fogelson<sup>37</sup> demonstrated that injections of homologous and heterologous sperm into female rats resulted in sterility of from 6 to 29 weeks' duration. He then tried to demonstrate agglutinins, lysins, or toxins in the sera and cervical secretions of 17 women classified as having idiopathic cases of sterility but was unable to find "sensitization to human spermatozoa protein." (The possibility that the



antigen(s) is nonprotein in nature was apparently not considered.) Also in 1926 Rosenfeld<sup>38</sup> took note of isolated, vague reports from birth control clinics which seemed to show that women who had been injected with semen could avert pregnancy for about 20 months. He, therefore, injected 3 female patients with human sperm, but was unable to demonstrate a definite positive test for spermatoxin in their sera although one of the patient's sera exhibited some antisperm immobilization activity. (He reported, incidentally, that a 29-year-old woman who was arthritic felt that her joint pains were relieved by the injections and requested that they be continued.) Mudd and Mudd<sup>39</sup> employed electrophoretic and complement-fixation methods to demonstrate that the sperm of man, guinea pig, bull, and ram injected into rabbits induced antibodies which were species specific. Cross reactions between bull and ram sperm and their corresponding antisera were also noted. Mudd and Mudd concluded that mammalian sperm possessed both species and tissue specificity.

Eiseman and Friedman<sup>40</sup> injected rats, rabbits, and guinea pigs with homologous sperm and obtained no immobilization reaction with the antisera of the rats and rabbits. In the case of the guinea pig, however, positive results were obtained. The toxic effect was removed by heating the sera to 56° C. Ardel<sup>41</sup> provided a partial review of the early literature to indicate his interest in the field and in experiments with female rabbits reported that injections of sperm resulted in a temporary sterility. Another possible factor in infertility was disclosed by Rosenthal,<sup>42</sup> who noted that certain strains of *Bacillus coli* caused the sperm of guinea pigs, rats, rabbits, and humans to agglutinate almost instantaneously. The active principle was nonfilterable and was destroyed by boiling (100° C.) but not by heating (60° C.). Other bacilli did not contain this factor. Guyer and Clause<sup>43</sup> prepared a nucleoprotein fraction from bull testis which, when injected into female rats, induced temporary or permanent sterility.

Lewis<sup>44</sup> disclosed that testicular tissue reacted with antibrain serum so well that no differentiation between the two tissues was possible. Moreover, antibrain sera reacted with no other organs than brain and testicle. In addition, antitesticle sera reacted only with brain and testicle and not with liver, lung, heart, spleen, kidney, or ovary. Thus the elaborate studies of Lewis have established that: (1) brain and testicle have common antigenicity; (2) brain and testicle do not exhibit a species specificity but, rather, a marked selectivity for each other. Wang<sup>45</sup> injected sperm of rats, dogs, or sheep into female rats and, although he was unable to confirm previous reports of induced sterility, he did find the sera of the injected animals to immobilize and agglutinate sperm.

In 1937, U. S. Patent number 2,103,240 was awarded to Baskin<sup>46</sup> for a nonspecific spermatoxic vaccine and for the process involved in producing the vaccine. The object of the invention was "the production from material obtained from the lower animals, of a determinant for human sperm and semen and usable as a vaccine or antigen in vaccination of human female to produce spermatoxic condition in her blood and secretions." Despite the twelve claims made in the patent, it is not recorded in the literature that the material has achieved the goals set forth.

Henle<sup>47</sup> supported the contention that species specificity of spermatozoa was of a dominant rather than absolute nature, for he found cross reactions between sperm of different species: there was a strong antigenic resemblance between bull and sheep, but less reactivity between bull and man. Also all rabbit anti-bull sera exhibited marked reactions with human sperm. Henle and his associates<sup>48</sup> conducted extensive studies on the antigenic nature of mammalian sperm and characterized especially the antigens of bull sperm: heat labile head-specific and tail-specific antigens and a heat stable antigen common



to both heads and tails which was species specific were observed. Using heterologous antisera, these workers revealed 3 different cross-reacting antigens in bull sperm: 2 were in the heads and one was located in the tails; one of the head antigens in bull sperm was not active in the native cell but was uncovered after rupture of the sperm.

Eastman, Guttmacher, and Stewart<sup>49</sup> were intrigued by the possibility of inducing sterility in females by means of sperm injections. They, therefore, undertook a 2 year study, using the rat as the experimental animal. The following observations were made: dog, horse, and ram testicular material was ineffective in altering fertility; rat sperm injected into 2 groups of females reduced by 40 and 73 per cent, respectively, the numbers of females which became pregnant. After following the fertility index in control females of various ages, however, they attributed the decline in fertility to the advanced age of the animals employed and, therefore, concluded that sperm injections reduced fertility slightly, but the effect was neither significant nor of practical importance. Parsons and Hyde<sup>50</sup> undertook an extensive study to evaluate the use of spermatotoxic sera in the prevention of pregnancy. Their conclusions were: (1) antibodies to ox, sheep, guinea pig, rat, and rabbit sperm can be demonstrated; (2) there was no evidence that pregnancy was prevented or delayed by treating rats or rabbits with sperm; (3) antibodies to guinea pig sperm were readily produced in the blood of rabbits by intravaginal injections; (4) intravaginal injection of immune guinea pig serum temporarily arrested fertility of rabbits; the uteri of rabbits immunized intravaginally were found to have antibody titers as high as in their blood serum. (The experiments of Parsons and Hyde were excellently conceived and executed, but from the point of view of immunology it should be kept in mind that the highly inbred strains of animals employed connote a high degree homogeneity; if an exacerbated immune response is desired, one generally seeks genetic heterogeneity.)

Henle and Henle<sup>51</sup> failed to induce temporary sterility in female mice by passive immunization with spermatozoal antisera. The same workers<sup>52</sup> immunized female guinea pigs with homologous sperm and obtained an antibody response in 60 to 77 per cent of cases but observed no decrease in fertility. (It is important to note that the spermatozoa were injected intraperitoneally. This route of administration is not so effective as the intradermal route in elevating antibody response.) Heterologous material (bull sperm) evoked antibodies in 100 per cent of female guinea pigs, but cross-reactivity with guinea pig sperm was weak and fertility was unaltered.

Lamoreaux<sup>53</sup> investigated the effects of injections of homologous sperm into laying hens in a manner similar to that employed by McCartney.<sup>29</sup> Despite the fact that high titers of sperm antibodies were demonstrable following injections of semen, Lamoreaux was unable to affect the fertility of the hens receiving these injections. (It should be recalled, however, that McCartney also found that the rate of egg production was not influenced by the injections: rather, the eggs layed for some time after injections were infertile. It could hardly be expected that sperm injections would alter egg production in hens [or other animals] but whether sperm injections can alter the number of fertilized eggs produced is quite another matter. Lamoreaux's experiments do not refute those of McCartney. Indeed, complete investigation of this important point with the hen as the experimental animal still remains to be done.)

Lewis<sup>54</sup> demonstrated that not only did antitestis sera react with brain tissue and vice versa but also that antisera against alcoholic extracts of these two organs had the same antigenic properties. Moreover, both organs showed otherwise complete organ specificity except for cross reactions with corpus luteum.

Antiplacental antibodies also must be included as culprits in cases of infertility: Cohen and Nedzel<sup>55</sup> concluded that antiplacental antibodies are capable of producing abortion, apparently by specific action on the placenta. The sera of 2 women known to be habitual aborters gave positive precipitin reactions with proteins prepared from full-term human placentas. These authors appear to have corroborated their contention that antiplacental antibodies could cause interrupted pregnancy by injecting preparations of full-term guinea pig placentas intramuscularly into rabbits, obtaining antiserum, and injecting the antiserum into pregnant guinea pigs. Abortion occurred in 5 of 6 animals 1 to 5 days following this treatment, and all fetuses were dead. Histologic examination of the aborted placentas revealed pathologic changes. Two pregnant guinea pigs injected with normal rabbit serum did not abort.

Brunner<sup>56</sup> immunized female rabbits with a "bull sperm phospholipid" suspended in sheep serum and found that, although fertility was unimpaired, a small but significant percentage of offspring were hermaphroditic. The material used by Brunner was provided by Dr. Istvan Sugar of Budapest. The claim made by Sugar was that 30 women treated with this antigen remained sterile for 6 months while continuing normal sexual relations. The "antigen" was obtained by treating epididymal sperm of young bulls in an unrevealed chemical process which resulted in a phospholipid. The phospholipid was suspended in sheep serum and Ringer's solution and put in 5 c.c. ampules, the amount necessary for one injection.

Burke and his co-workers<sup>57</sup> have reported antigens in chick embryos which resembled antigens of the adult sex organs, and Cooper<sup>58</sup> has indicated antigens in eggs, embryos, and larvae of frogs which seemed closely related to those of adult sperm. Smith<sup>59</sup> provided evidence of the antigenic properties of mammalian spermatozoa and demonstrated different types of agglutination of sperm by antisperma antisera.

Docton and collaborators<sup>60</sup> presented evidence that bovine isoimmune sera containing antibodies for bovine erythrocytes also reacted specifically with bovine sperm. Also when antibovine sperm antibodies were produced in sheep, specific lysis of erythrocytes of certain cattle was observed coincidentally with agglutination of bovine sperm. These authors theorized that antigens recognizable in bovine erythrocytes have similar or identical counterparts in sperm.

At about this time (1950) adjuvants were gaining recognition for their ability to potentiate antibody response and Voisin, Delaunay, and Barber<sup>61</sup> recorded testicular damage in guinea pigs injected with homologous testicular homogenate in adjuvant.

Freund, Lipton, and Thompson<sup>62</sup> established that autologous or homologous testicular material incorporated into adjuvant induced selective destruction of the spermatogenic tissue in guinea pigs. The same workers also reported<sup>63</sup> impairment of spermatogenesis in rats injected with homologous testis plus adjuvant. From the same laboratory<sup>64</sup> attempts to induce aspermatogenesis in guinea pigs by means of heterologous testicular material and by means of extracts of guinea pig testicles were recorded. The following results were obtained: testis or sperm from bull, rabbit, hamster, or sheep failed to induce aspermatogenesis in the guinea pig, even though adjuvants were employed; after treating testes with various chemicals, the authors obtained an antispermatic agent. Voisin and Delaunay<sup>65</sup> extended and confirmed their findings that aspermatogenesis could be induced by immunologic means.

Meanwhile, the work of Wilson<sup>66</sup> advanced another aspect of male infertility when he demonstrated that agglutination of normal human sperm was produced by the seminal plasma and blood serum of 2 patients whose spermatozoa exhibited autoagglutination. This work has been carried further by

Wilson<sup>67</sup> and by Weil and associates.<sup>68</sup> In the former study, a third case history of agglutination due to autoantibody is presented along with immunologic findings. Moreover, it was revealed that the wives of the 2 infertile men conceived promptly after AID (artificial insemination by donor). In the study of Weil and his co-workers, the findings were interpreted as indicating that seminal plasma contains highly antigenic material which is distinct from that of sperm. Indeed, these authors suggest that the antigenic material found associated with human sperm originates from the accessory organs of reproduction rather than from the testes. (This would mean that human sperm is not antigenic, and, in view of the evidence indicated previously, this suggestion is a startling one. It requires unequivocal proof, however, to be accepted at this time.)

Austin<sup>69</sup> has demonstrated that the supernumerary spermatozoa in the uterus of mice are removed by phagocytosis. The implications of this work in connection with a mechanism whereby the female is rendered sensitive to sperm are obvious. After the demonstration of uterine anaphylaxis following sensitization to sperm in experimental animals,<sup>70</sup> it was pointed out that macrophagic ingestion of sperm could be the initial step in sensitization of the female to sperm.<sup>71</sup> The mechanism of immunization involved in isoallergic disorders (including aspermatogenesis) has been presented in the form of a hypothesis,<sup>72, 73</sup> and the fundamental stimulus underlying smooth-muscle contraction during anaphylaxis has also received attention.<sup>74</sup>

### Comment

In presenting the foregoing material, it has been the purpose of the author to permit the evidence to speak for itself in answer to the question as to whether or not problems of fertility or sterility might have immunologic interpretations. It is fitting, however, to present an opinion at this time. Based only upon the evidence presented, it appears that some problems of infertility may be interpreted on an immunological basis and, thus, may provide a clue to the control of fertility. As has been indicated in the foregoing, this thought is not new since it has been expressed repeatedly in the last 50 years. What is important to know at this time is how to utilize the information in regard to the control of fertility. It is obvious that several lines of attack may be undertaken:

1. The observations by Landsteiner, Metchnikoff and Metalnikov and those of Voisin and Freund and their associates might be employed in the preparation of vaccines to be tested for use in human beings.
2. The possibility of making and employing an antiplacental vaccine, as the work of Cohen and Nedzel might be interpreted as suggesting, should be investigated.
3. The demonstrations by Wilson, Weil and co-workers that secretions of the accessory organs of reproduction are antigenic should be explored for the possibility of preparing an antisecretory vaccine.
4. If ova can be made antigenic, the use of such material in a vaccine should receive attention.

These suggestions have considered the male and female gametes as well as the secretions of the accessory reproductive organs of the male. It remains to be determined whether secretions of the accessory organs of reproduction of the female may also require attention. In addition, recently we<sup>75</sup> have been able to



demonstrate that hyaluronidase, when incorporated into adjuvant and injected into the guinea pig, results in sensitization of the animal as shown by challenging the isolated organs of the animal with specific antigen. This information may also have important implications.

As to the mechanism whereby the various vaccines may act in the control of fertility, one can only speculate at this time. The following possibilities exist: (1) Immunization with sperm may lead to antibodies which will cause cytolysis of sperm, or the antibodies may induce precipitation, aggregation, or immobilization of sperm. (2) Immunization with placental antigen might inhibit or prevent formation of the placenta and if the antigen could be derived from very early placentas, inhibition of placental formation might be possible very early in gestation. (3) A vaccine of antigen prepared from accessory organs of reproduction of the male might influence fertility by causing precipitation of the secretory products in the female tract and thus provide an environment hostile to the sperm.

In the foregoing cases, as well as that of antihyaluronidase vaccine, the introduction of more antigen during subsequent copulations would be expected to maintain antibody levels. With regard to an antiova preparation, even though it has not been found that ova are antigenic (apart from the report of Ricketts,<sup>14</sup>) yet it is possible that some method such as complexing with haptens can make them so. If an antigen to mature ova can be prepared, it would have the advantage of leaving immature ova unaffected.

At the same time that mechanisms of action of the vaccines are discussed, it is clear that these may well be the responses which occur normally in certain inexplicable cases of infertility: for example, it is not unlikely that certain cases of spontaneous abortion may be due to a prior sensitization to placental antigens during the course of a first pregnancy in which placental damage had occurred. The sensitization could lead to the formation of antibodies which could cause damage to the placenta during subsequent pregnancies.

*Addendum.*—While this manuscript was in press, Isojima, Graham, and Graham<sup>76</sup> published a paper in which it was recorded that only 24 per cent of female guinea pigs remained fertile after injection with homologous testis in Freund's adjuvant. This was a significant decrease in fecundity since 84 per cent of the control animals were fertile. This report confirms our previous findings with guinea pig testis.<sup>77</sup> In other experiments, for example, injections of homologous seminal vesicle and prostate in adjuvant had no effect on fertility in female guinea pigs, whereas injections of homologous brain and ovary as well as testis did inhibit fecundity in female guinea pigs.<sup>78</sup> The paper of Isojima and co-workers<sup>76</sup> receives further consideration in a report dealing with the induction of infertility in female guinea pigs by injection of homologous sperm.<sup>79</sup>

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## CARCINOMA IN SITU OF THE CERVIX

### A Clinical Review of 842 Cases

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THE past 10 years have witnessed an important advance in the attempt to control cancer of the cervix. This is the acceptance of the fact, first recognized more than 30 years ago, that neoplasia of cervical epithelium can be detected microscopically before its potential invasiveness is manifested. The recent literature reflects increasing agreement on this once controversial point of view but indicates that divergent opinions remain concerning proper methods of diagnosis and treatment.

The experience of the Mayo Clinic in the management of carcinoma in situ of the cervix dates from 1932 when the diagnosis was made in one patient and the lesion was controlled by the application of radium. Since that time diverse methods of treatment have been used in an ever-increasing number of cases. This study was undertaken to evaluate the appropriateness and adequacy of treatment as well as to delineate certain features of the disease which may be of clinical or pathologic interest.

#### Selection of Cases

Included in this review are 842 cases of carcinoma in situ of the cervix in which the diagnosis was made and treatment was carried out at the Mayo Clinic from Jan. 1, 1932, through Dec. 31, 1957. An additional group of 147 cases was discarded for the following reasons: (1) The diagnosis was made but treatment was not carried out at this clinic (47 cases). (2) The diagnosis was confirmed at this clinic by review of the original slides, but treatment was given by another physician prior to admission (35 cases). (3) The diagnosis was not sustained at the time of recent review of available slides or specimens or both (10 cases). (4) The pathologic diagnosis of carcinoma in situ was negated by an indisputable clinical diagnosis of invasive cancer (29 cases). (5) Early stromal invasion was found in the excised uterus (25 cases). (6) The excised uterus showed no residual carcinoma and a slide of the original biopsy specimen was not in our files (one case).

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### Clinical Features of Series

**Incidence.**—Frequency of diagnosis by year is indicated in Fig. 1. The doubled incidence from 1950 to 1951 reflects the adoption in 1950 of a policy of making a cytologic spread from the cervix of every patient, 30 years of age or more, who was examined in the department of obstetrics and gynecology and from the cervix of younger patients if a suspicious-appearing lesion was present. Subsequently the age limit for this routine procedure was dropped to 25 years, and in 1956 and 1957 routine use of the smear was gradually extended to include all women more than 25 years of age who registered for a general physical examination. This broadening of the effort to detect early carcinoma of the cervix is reflected in Fig. 1 by the marked increase in number of cases in 1957.

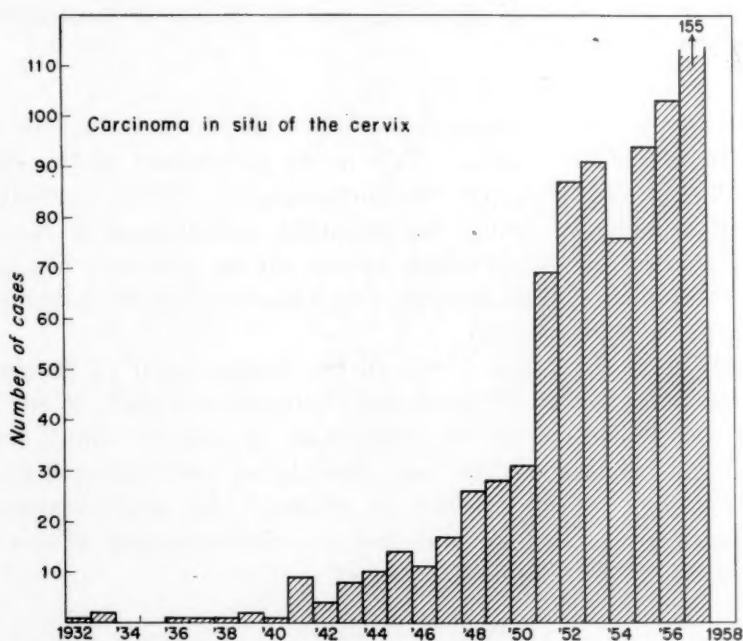


Fig. 1.—Incidence of carcinoma in situ of the cervix by years from 1932 through 1957.

**Age.**—The ages of the patients ranged from 19 to 79 years, with a mean of 43.4 years. The distribution of the ages in 5 year groups is shown in Fig. 2. The mean age of 257 patients seen in 1956 and 1957 was 45.0 years as compared with the mean age of 42.7 years of all patients seen prior to 1956. The mean age of patients with invasive carcinoma of the cervix treated at the clinic between 1940 and 1950 was 49.0 years.<sup>1</sup> Obviously, these figures do not support the widespread belief that carcinoma in situ of the cervix reaches its maximal incidence about 10 years earlier than does invasive carcinoma. Perhaps they merely reflect the fact that the average age of all female patients registered at the clinic is 44 years and that clinic or hospital populations are selected groups which do not justify valid assumptions concerning age or population distribution of any disease.

**Marital Status.**—The relative infrequency of cancer of the cervix in unmarried women has been pointed out previously<sup>2</sup> and is borne out by our figures concerning marital status at the time the diagnosis was made. Only



33 women were unmarried; 728 were married, 42 were divorced, and 39 were widowed. No effort was made to record pleural marriages.

*Obstetric History.*—Sufficient data were lacking to determine gravidity with accuracy, but it appeared that 148 women had never been pregnant, 165 had had one pregnancy, 441 had had two to five pregnancies, and 74 had had more than six. No information regarding the obstetric history was present in 14 case records. A separate classification of abortions, ectopic gestation, and full-term pregnancy was not attempted.

*Previous Treatment of the Cervix.*—The records were grossly inadequate with respect to this point. Only 29 patients were said to have had cautery to the cervix prior to their current illness, and the extent of treatment is unknown. Two patients had undergone amputation of the cervix 2 and 12 years,

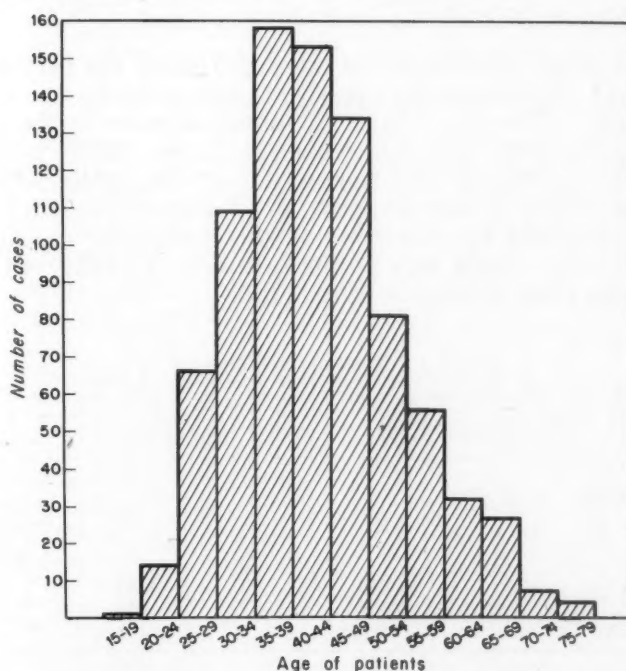


Fig. 2.—Ages of patients with carcinoma in situ of the cervix.

respectively, prior to the diagnosis of cancer. Too few patients had had previous biopsies at the clinic to permit any significant conclusions. In no instance was cancer found in later review of the earlier slides.<sup>3</sup>

*Previous Irradiation.*—A history of previous radium or roentgen therapy was obtained from only 10 patients. Four women had undergone diagnostic curettage and intrauterine insertion of radium 6 to 15 years before admission. One patient had had carcinoma of the ovary 4 years previously and had been treated by subtotal hysterectomy and salpingo-oophorectomy followed by external irradiation. In one case, roentgen therapy had been given 3 years previously because of an ovarian "cyst." Two patients had received limited roentgen therapy for ovarian failure 16 years before discovery of carcinoma of the cervix. One patient had just completed a 4 week course of external irradiation but is included in this study because of the presence of carcinoma in situ in the cervix

at the time of hysterectomy at the clinic. The last patient had received two treatments with roentgen rays 3 months before admission, but the indications for this procedure are not known.

Four patients had worn intravaginal pessaries, 2 for 3 and 4 years, respectively, and the other 2 for an unknown length of time.

*Presenting Complaint.*—More than half of the patients (529) sought medical advice because of symptoms referable to systems other than the reproductive tract. One hundred twenty-two patients had gynecologic complaints, such as infertility or dysmenorrhea, that were considered to be unrelated to carcinoma of the cervix. Abnormal vaginal bleeding or discharge had been noted by 135 patients; however, it was not assumed that the neoplasm was responsible for the symptom. In 56 cases, a malignant lesion of the cervix had been suspected or proved prior to admission and the patient did not state the reason for which she initially consulted a physician.

*Reasons for Biopsy.*—Inasmuch as investigation of the cervix was justified in only 15 per cent of patients because of symptoms alone, the indications for biopsy were sought. We found that 133 patients came to the clinic because of suspected or proved carcinoma in situ (Table I). In 28 instances, only a positive or an abnormal smear had been obtained. A positive biopsy had been secured from the cervixes of 105 patients. Slides from 90 of these biopsy specimens were reviewed by members of the section of surgical pathology at the clinic and were found to contain cancer. The other 43 patients had confirmatory biopsy after admission to the clinic.

TABLE I. REASONS FOR BIOPSY

REASON	CASES			TOTAL
	1932-1955	1956-1957		
Diagnosis suspected or proved before admission				
Smear only	21	7	28	133
Biopsy	79	26	105	
Lesions or symptoms	248	32		280
Abnormal smear	203	160		363
Biopsy not performed	33	33		66
Total	584	258		842

Histologic investigation of the cervixes of 280 patients was thought advisable either because of the appearance or because of unexplained bleeding. Smears positive for cancer (hereafter called a positive smear) led to the ultimate diagnosis of carcinoma in situ in 363 patients. The credit for diagnosis was given to the smear only when the cervix was described as normal or when its appearance was so innocuous that biopsy was not advised unless the smear was positive. The Schiller test has been employed to assist in delineating the proper site for securing biopsies, but not consistently enough to be of value in this study.

A diagnosis of carcinoma in situ was not made prior to operation in 72 cases as shown in Table II. (In no instance was irradiation begun in the absence of a tissue diagnosis.) The lesion was an incidental finding in 24 cases, the uterus having been removed for an indication other than cancer. Six patients had at least one cytologic smear positive for carcinoma, but all biopsies were negative at the time of hysterectomy. The remaining 42 had

had positive smears, but no tissue sections had been prepared prior to primary hysterectomy or excision of the cervical stump. Thirteen of these patients needed hysterectomy because of relaxation of the vaginal outlet or because of a pelvic tumor but the remaining 29 were operated on without any indication of cancer other than that in the smear.

TABLE II. DIAGNOSIS OF CARCINOMA IN SITU NOT MADE BEFORE OPERATION, 72 CASES

	CASES		
	1932-1955	1956-1957	TOTAL
Incidental findings	23	1	24
Positive smear; negative biopsy	3	3	6
Positive smear; no biopsy	10	32	42
Other indication for operation	3	10	13
No other indication for operation	7	15	22
Stump removed as biopsy		7	7
Total	36	36	72

### The Cytologic Smears

The cervical smear for cytologic examination was first used at the Mayo Clinic in 1947. Three years later, as previously noted, the technique was made applicable to the majority of women, age 30 years or more, who were examined in the department of gynecology and obstetrics. The years 1947 through 1957 yielded 777 of the cases in the study. The results of the examination of smears made from the cervix in these cases are grouped according to the method of Papanicolaou in Table III.

TABLE III. SMEAR TESTS ON PATIENTS SEEN FROM 1947 THROUGH 1957

	1947-1949	1950-1955	1956-1957	TOTAL CASES
No test	46	33	13	92*
Results of tests:				
Negative	5	27	9	41
Unsatisfactory	4	7	2	13
Group 2	0	5	0	5
3	2	102	78	182
4	1	106	56	163
5	13	168	100	281
Total	71	448	258	777

\*The test was not done because biopsy was indicated by a lesion or symptoms in 41 cases; diagnosis was established before admission in 36 cases, and carcinoma in situ was an incidental finding in the remainder.

Only the initial smear obtained at the clinic in any case was used in the tabulation because that is the most important one from the aspect of the clinician, who, should he obtain a negative report in the presence of a cervix which appears to him to be normal or nearly so, is unlikely to subject the cervix to further study. It is significant, therefore, that 41 (6.0 per cent) of the primary smears in the 685 cases in which smears were taken showed no malignant cells.\* The misleading impression created by the initial negative smear, however, frequently was corrected by tissue biopsy which showed carcinoma in situ. Thirteen smears were unsatisfactory for study.

From 1950 through 1957 there were 45 instances of negative or unsatisfactory smears (Table IV). The initial biopsy at the clinic in 33 of these

\*Biopsy had been performed on 11 of these 41 cervixes prior to admission of the patients to the clinic. If these 11 are excluded, a false negative report was rendered in 4.4 per cent of the primary smears.

cases showed carcinoma in situ. In 7 cases the initial biopsy at the clinic was also negative for cancer, but suspicion had been directed toward the cervix by a positive smear (3 cases) or biopsy (4 cases) prior to admission. No residual malignant lesion was found in the excised uterus in 3 of the latter patients, but carcinoma in situ was found at operation in the cervix of the other 4 patients in this group of 7. In 4 other patients in the group of 45 whose initial smears at the clinic were negative, a positive biopsy before admission was the basis for operation. For the last patient, a second smear was made; this proved to be positive and biopsy was done.

TABLE IV. DATA ON 45 CASES IN WHICH INITIAL SMEARS WERE NEGATIVE OR UNSATISFACTORY

	NO. OF CASES	
Initial biopsy at clinic positive		33
Initial biopsy at clinic negative		7
Positive smear before admission	3	
Positive biopsy before admission	4	
Operative finding:		
No residual neoplasm in uterus	3	
Residual neoplasm present	4	
No biopsy at clinic; previous biopsy positive		4
Operative finding:		
No residual neoplasm found	2	
Residual neoplasm present	2	
Second smear at clinic positive		1
Total		45

At times the initial smear is positive for malignant cells, but carcinoma is not found in the first biopsy. This occurred in 38 cases and was undoubtedly due to inadequate sampling. This dilemma is usually solved in a satisfactory manner by surgical, cold knife conization of the cervix. Rapid examination of sections of the specimen prepared by the fresh-frozen technique allows the pathologist to return a diagnosis within a few minutes in most cases and permits a prompt decision by the surgeon regarding proper treatment.

#### Carcinoma in Situ Not Found at Operation

No residual carcinoma was found in the cervixes of 158 (20.3 per cent) of the 786 patients treated surgically. This figure includes the cases in which specimens were obtained by conization but not those in which the uteri were removed immediately subsequent to conization. The records indicate that office biopsy had been the only procedure carried out in 47 of these patients, hemostatic or therapeutic cauterization had been done in an additional 77 patients, and conization or amputation had been done prior to admission in 5. The case records of the remaining 29 were not sufficiently detailed to show whether cauterization had accompanied the office biopsy.

In recent years, the gynecologist has shown a laudable tendency to refrain from thermal destruction of cervical lesions until a negative smear or biopsy report or both are available. This is reflected by the fact that residual carcinoma was not detected in the cervix of 57 (38.5 per cent) of 148 surgical specimens up to 1950 and was absent from only 69 (17.9 per cent) of 385 specimens obtained during the ensuing 6 years and from only 32 (13.0 per cent) of 247 specimens in 1956 and 1957. This trend for the years 1941 through 1957 is depicted in Fig. 3.

#### Carcinoma in Situ in the Cervical Stump

Carcinoma in situ was found in the cervical stump in 61 patients who had undergone subtotal hysterectomy from 2 to 36 years previously. This is 7.2



per cent of the total of 842 cases, an incidence closely comparable to that of invasive carcinoma in the cervical stump.<sup>4, 5</sup> In 30 cases, the operation had been done 11 or more years before the diagnosis of carcinoma in situ was made. Fifteen patients had been operated on 6 to 10 years before the diagnosis of carcinoma in situ, and the remaining 16 patients less than 6 years before. In 8 cases of the last group, only 2 or 3 years had elapsed between subtotal hysterectomy and the finding of carcinoma of the cervix. It is possible, in these 8 instances at least, that carcinoma was present in the cervix and was overlooked at the time of the previous operation.

### Associated Lesions

*Benign Lesions.*—Leukoplakia of the cervix was an associated pathologic finding in 66 cases and was noted only by the clinician in 7 additional cases. In 2 cases, leukoplakia of the vaginal wall was present; in one of these, there was also basal-cell hyperactivity, and in the other, carcinoma in situ underlying the leukoplakia.

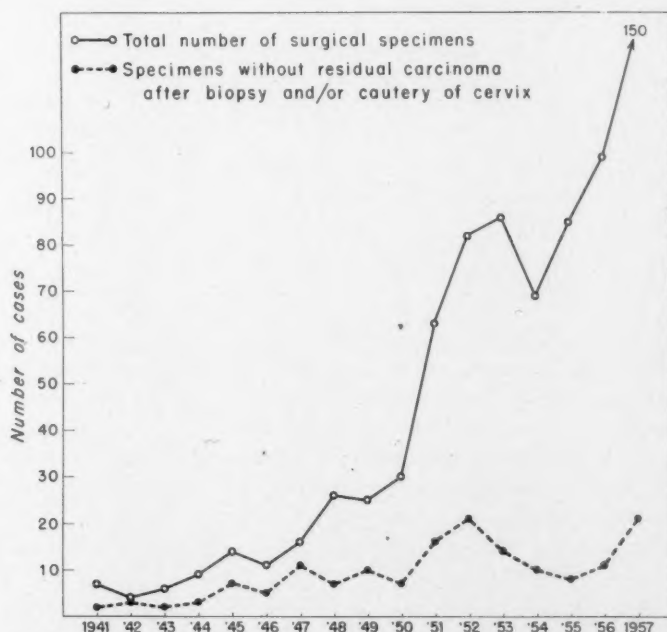


Fig. 3.—Distribution by years of cases in which no residual carcinoma was found at operation after biopsy or cautery of the cervix or both.

Polyps were present in the cervixes of 59 patients. In 15 instances (25 per cent) the pathologist expressly stated that carcinoma was present in the polyp. The remaining polyps appear to have been incidental, but by their presence they probably contributed significantly to the detection of the underlying cancer. Patients with such polyps are usually referred to the gynecologist and hence the routine smears are made.

*Carcinoma of the Vagina or Vaginal Cuff.*—Involvement of the vaginal cuff by carcinoma in situ was observed in 13 cases, in all but one of which the vaginal lesion was concurrent with the lesion in the cervix (Table V). In 9 instances, discovery of the malignant lesion in the vaginal wall was made at the time of operation for the cervical lesion. In 3 cases, it was recognized at retrospective review of the specimens. One of these 3 patients had carcinoma in situ in a small area of the vault 3 years after abdominal hysterectomy. A

second patient had invasive carcinoma of the vagina, proved and treated at another institution, 10 years after abdominal hysterectomy. The third patient had vaginal bleeding approximately 5½ years after vaginal hysterectomy. Subsequently she received at least two courses of roentgen therapy at another institution. Unfortunately no tissue studies were done, but the presence of invasive carcinoma must be assumed.\* The thirteenth patient was found to have carcinoma in situ of the vagina 10 months after total abdominal hysterectomy had been done for carcinoma in situ of the cervix. Re-examination of the vaginal cuff revealed basal-cell hyperactivity and dysplasia extending to the line of excision.

TABLE V. CARCINOMA IN VAGINA: DISCOVERY IN RELATION TO OPERATION FOR CARCINOMA IN SITU IN CERVIX

	NO. OF CASES
Simultaneous carcinoma in situ in vaginal cuff and in cervix discovered:	
At operation for cervical lesion	9
On review of specimen removed at operation for cervical lesion because of:	
Invasive carcinoma of vagina 10 years later	1
Carcinoma in situ in vagina 3 years later	1
Unknown type of lesion in vagina 12 years later	1
Subsequent carcinoma in situ in vagina discovered:	
After hysterectomy for carcinoma in situ of cervix; review of specimen removed then revealed only basal-cell hyperactivity and dysplasia of vaginal cuff to line of excision	1
Subsequent invasive carcinoma of vagina	
No vaginal biopsy before radium to cervix	1
Vaginal cuff negative	1
Total cases	15
Total carcinoma in situ in vaginal cuff	13

Invasive carcinoma of the vagina developed subsequent to treatment of carcinoma in situ of the cervix in 2 patients. The first had a vaginal hysterectomy in 1937 because of cystocele and uterine descensus. The cervix was reported to show chronic cervicitis. In 1940, because carcinoma of the vaginal vault was proved by biopsy, the cervix was re-examined and reported to contain carcinoma in situ. More recent study of the vaginal cuff has shown it to be free of carcinoma. The other patient, aged 73 years, received radium treatment of carcinoma in situ of the cervix. Six months later biopsy showed invasive carcinoma of the vagina.

*Other Malignant Lesions.*—Seventy-one of the patients in this series had malignant lesions in locations other than the cervix. One of these patients had five neoplasms and 9 of them had two, making a total of 84 tumors. The distribution of these lesions and their temporal relation to the cancer of the cervix are given in Table VI. The incidence of multiple malignant lesions is no higher than that reported in other series of cancer patients<sup>6</sup> and, even if it were higher, it might reflect only increasing efficiency of diagnosis in a select group rather than a significant predilection of these individuals to form neoplasms.

#### Association With Pregnancy

Fourteen patients were pregnant at the time the diagnosis of carcinoma in situ was made; 11 were in the first trimester of pregnancy, 2 in the second, and 1 in the third. Only 4 patients were more than 30 years of age, and the youngest was 20. Hysterectomy was performed in 10 cases, in 2 of which the

\*In January, 1959, this patient returned to the clinic. Biopsy of a lesion in the vaginal vault showed infiltrating carcinoma of the same grade as the carcinoma in situ removed at hysterectomy 14 years previously.

ovum was located in the tube. In one case dilatation and curettage was done at the time of therapeutic conization of carcinoma in situ, and placental tissue was recovered. Three pregnancies were not interrupted. In the first of these 3 cases, carcinoma in situ was discovered at about the sixth week of pregnancy, but no treatment was given. Subsequent biopsies, at the time of delivery and again 6 weeks and 4 months post partum, confirmed the diagnosis; hysterectomy was performed. The second patient was delivered vaginally at term 10 days after carcinoma in situ was found in the cervix. At the time of conization 10 weeks later no residual neoplasm was detected. The last patient was found to have carcinoma of the cervix when she was in the second month of pregnancy. The uterus was removed 9 weeks after delivery, but no residual malignant lesion was present.

TABLE VI. MALIGNANT LESIONS ASSOCIATED WITH CARCINOMA IN SITU OF THE CERVIX

SITE	TIME OF DIAGNOSIS IN RELATION TO DIAGNOSIS OF CARCINOMA IN SITU OF THE CERVIX			
	PRIOR	SIMULTANEOUS	SUBSEQUENT	TOTAL
Cervix and corpus (adenocarcinoma)		7		7
Vagina		12	6	18
Vulva	5	3		8
Breast	8	5	2	15
Ovary	1	1		2
Gastrointestinal tract	6	3	1	10
Miscellaneous	14	8	2	24
Total	34	39	11	84

Six patients were found to have carcinoma in situ of the cervix after the termination of gestation. In one patient, biopsy was positive for carcinoma at the time of completion of a spontaneous abortion by dilatation and curettage; hysterectomy was done. In another, previous suspicious-appearing smears led to biopsy at the time of full-term delivery; vaginal hysterectomy was carried out 3 weeks later. In the other 4 cases the diagnosis of carcinoma was made approximately 2 months post partum: in 3 after a term pregnancy and in one after spontaneous abortion. Three were treated by hysterectomy and one by conization.

Six patients in this series have been gravid subsequent to diagnosis and treatment of Stage 0 (International classification) carcinoma of the cervix. Their ages, type of treatment, parity at the time of the diagnosis and number of later pregnancies are given in Table VII.

TABLE VII. PREGNANCY SUBSEQUENT TO TREATMENT OF CARCINOMA IN SITU, 6 CASES

AGE (YEARS)	PARITY WHEN CARCINOMA WAS FOUND	TREATMENT	SUBSEQUENT DELIVERIES
19	0	Cautery	1
21	i	Conization	3
22	i	Conization	2
29	0	Amputation	3
25	i	Cautery	1
20	0	Conization	1

### Treatment

The multiplicity of methods of dealing with carcinoma in situ mirrors the changing concepts and, at times, uncertain attitudes held by pathologist and clinician. Although certain trends in treatment are developing, it was

surprising to discover that 10 different categories of management appear for the year 1955 and no more than three to six for the years 1932 through 1950.

The various therapeutic measures employed and the total number of patients so treated are indicated in Fig. 4. Surgical removal of the uterus or its stump has virtually paralleled in frequency the annual incidence of carcinoma in situ since 1943 (Fig. 5).

Irradiation was employed as the sole treatment in 38 cases. Radium was used alone in 27 and combined with roentgen therapy in 11. In 11 additional cases, irradiation was used either before or after operation. Eight of the patients who received a full course of internal and external irradiation were initially considered to have invasive carcinoma. They were included in this series because the histologic findings and clinical description failed to support a diagnosis other than Stage 0 cancer. We are aware, however, of the fact

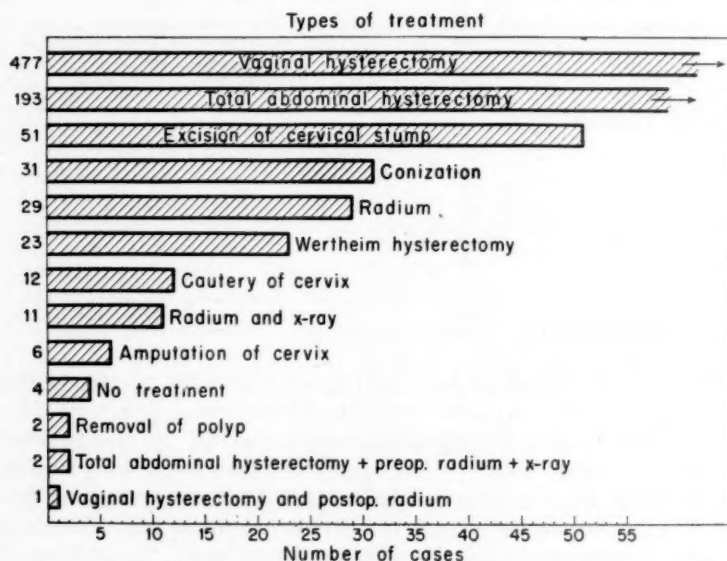


Fig. 4.—Treatment of carcinoma in situ of cervix.

that absolute proof of the absence of invasion is lacking unless a conization or hysterectomy specimen of tissue is available. All but 2 of the patients treated with radium only were seen in the final 7 years of the study. Indications for the application of radium in these last 25 cases included the following: associated serious disease, such as myocardial infarction and residual hemiplegia in 13 cases; other malignant lesions in 5; old age or general debility in 5, and miscellaneous conditions in 2. In general, it was thought that these individuals would tolerate a limited dose of radium better than a surgical procedure and general anesthesia.

Perusal of the statistics concerning operative cases supports the impression that treatment has become less radical. The Wertheim operation, either classic or modified, was employed in 17 (nearly 16 per cent) of the total of 107 patients treated prior to 1949. During the next 9 years it was performed but 5 times. The converse of this trend is shown by the figures with regard to conservative measures. Fifty-three patients, a small fraction of the total number of patients, were treated by various methods of local removal, but only 5 of these were seen prior to 1949, the majority (44) being treated in 1952 or later. The reasons for limited treatment can be divided into several



groups: attempt to preserve fertility for 17 patients; other serious disease in 6, including 4 with simultaneous malignant lesions; old age in 2; delayed diagnosis of carcinoma in situ and subsequent negative smear and biopsy in 11, and limited extent of lesion in 6. Two patients did not believe the diagnosis and refused treatment other than cauterization of the cervix incident to securing a biopsy. In 8 instances the indication for limited treatment was not apparent from a review of the records. In one case technical obstacles prevented removal of the cervical stump.

Four of 842 patients studied were not advised to have treatment for the lesion of the cervix. One had a squamous-cell carcinoma of the nasopharynx; another, bronchogenic carcinoma with metastasis; a third, terminal lymphoma.

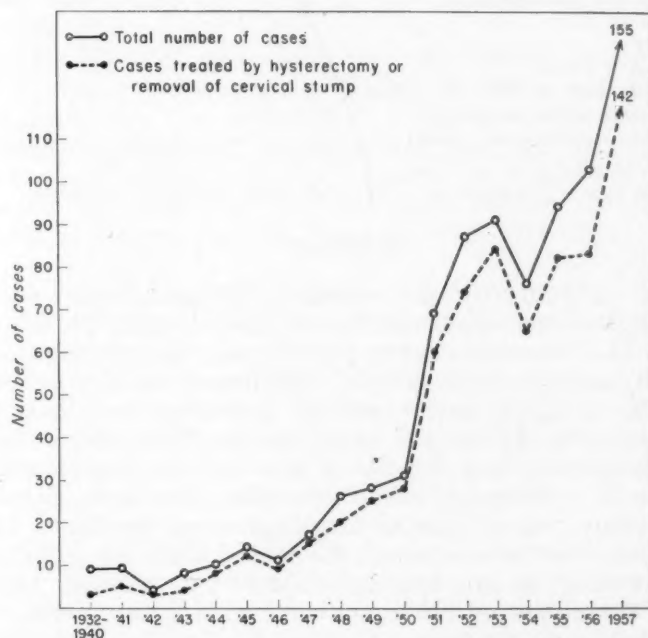


Fig. 5.—Carcinoma in situ of the cervix in cases in which hysterectomy or removal of the cervical stump was performed as compared with the whole group.

The fourth underwent extensive surgical biopsy which yielded only one tiny microscopic malignant focus believed to be too small to require additional treatment. These cases, of course, are in addition to the patients mentioned previously who were advised to have treatment but left the clinic without doing so.

### Follow-up

Letters of inquiry were sent to all patients who were treated before 1956, and who had not been examined at the clinic in 1957. The status of these 584 patients in January, 1958, is shown in Table VIII. The patients in whom carcinoma of the vagina was discovered later have been previously mentioned (Table V). Three must be regarded as being treatment failures due to lack of recognition of the extent of the carcinoma in situ and consequent excision of an insufficient cuff of vagina. The fourth failure resulted either from a poor response to radium of a preinvasive carcinoma or from inadequate biopsy of the initial lesion, resulting in its being classified as carcinoma in situ

instead of as Stage I carcinoma. In the 2 other patients with subsequent carcinoma of the vaginal vault, the vaginal cuff was apparently not involved by the cervical lesion and the tumor could not be considered recurrent.

TABLE VIII. TREATMENT FOR CARCINOMA IN SITU OF THE CERVIX (1932-1955): FOLLOW-UP DATA IN 584 CASES

	NO. OF CASES
No follow-up	23
Follow-up data	561
Dead	
Unrelated cause	34
Hospital death	1
Carcinoma of vagina	1
Apparently free of disease	
10 years or more	62
5-9 years	233
Less than 5 years	226
Known recurrence at time of follow-up	4
Recurrence treated elsewhere*	2
Recurrence treated at clinic†	2

\*Known to be living.

†Treatment too recent (September, 1957, and April, 1958) to evaluate.

### Comment

Detection of carcinoma of the cervix in the preinvasive and potentially curable stage requires the application of techniques other than simple inspection. As Carter and associates<sup>7</sup> have pointed out, the cervical lesions in 88.5 per cent of 275 patients with proved carcinoma in situ were considered "benign" prior to cytologic and histologic examination. In our series, the carcinoma was found in 363 cases largely because of the evidence in the smear, and in more than half of these the cervix was described as "normal," "clean," "senile," and so on. Younge<sup>8</sup> has emphasized that such descriptions frequently are not supported by careful visualization of the cervix after staining with Gram's iodine solution. Indeed, he stated that the Schiller test is as valuable for screening as are cytologic spreads or random biopsies in the patient without symptoms or other evidence of a gross lesion.<sup>7, 9-11</sup> Others place greater reliance on the smear than on the Schiller test. It is essential always to bear in mind that a negative smear does not eliminate the possibility of cancer,<sup>7, 8</sup> particularly if an obvious abnormality is present. The clinician may fail to secure cells from the squamocolumnar junction or may submit a smear that is unsatisfactory because of excess blood or improper preparation. The accuracy of a pathologist is, in part, proportional to the quality of the slides he receives; hence in any case in which a smear is reported to be unsatisfactory, the procedure should always be repeated. Likewise a smear which exhibits Group 2 or 3 cells (benign or suspicious appearing) should not be considered to be of less potential significance than one containing cells of Group 4 or 5 (probably or definitely malignant). We do not agree with de Alvarez<sup>12</sup> that a "suspicious" (Group 2 or 3) smear must be regarded as a "false negative" if the simultaneous biopsy is positive. Regardless of the degree of cellular atypia, an abnormal smear requires that the presence or absence of cancer be proved histologically. To some degree, the grouping of smears is a "personalized" function of each laboratory, and the precise interpretation of smears in Groups 2, 3, and 4 varies from one pathologist to another. It must be emphasized that 50 to 60 per cent of lesions of carcinoma in situ have associated areas of dysplasia or basal-cell hyperactivity<sup>13</sup>; hence, smears which reflect such epithelial abnormalities should prompt especially

thorough biopsy and histologic study. In our laboratory 51 per cent of the Group 3 smears are proved to be associated with carcinoma in situ, and 62 per cent of so-called false suspicious smears are associated with some degree of cellular atypism in the tissue sections.<sup>14</sup>

Multiple punch biopsies obtained in the office may be helpful in many cases<sup>7, 15</sup> especially if an obvious lesion is present. However, conization is elected as a primary procedure by some of our staff as well as by others<sup>16-18</sup> in order to eliminate the confusion introduced by negative biopsies and by failure of any biopsy to establish without doubt the noninvasive nature of a lesion. For the latter reason, cold knife conization biopsy is gradually becoming almost routine immediately prior to planned hysterectomy for apparent carcinoma in situ. If invasion is demonstrated, radical surgical measures can be carried out or the operation can be abandoned in favor of treatment with irradiation.

Surface extension of carcinoma into the mucous glands has not been regarded as evidence of invasion, and thus far the results appear to sustain this point of view. On the other hand, minimal microscopic involvement of the stroma has been classified (by definition) as Stage I cancer and has been excluded from this review. There is reason to believe, however, from the work of Carter and associates<sup>7</sup> and our own studies that these lesions can be managed in the same way as those of Stage 0 without jeopardizing the patient.

Leukoplakia has been noted often enough to support our contention that it is frequently associated with carcinoma in situ, especially when the leukoplakia is at or near the squamocolumnar junction.<sup>8</sup> This is at variance with the opinion of Novak and Novak<sup>19</sup> who relegated leukoplakia to an unimportant status among cervical lesions, stating, "The incidence of abnormal epithelial change does not appear high. The term leukoplakia as applied to microscopic degrees of cervical hyperactivity is just about passé. . . ."

Of great prognostic significance is the appearance of carcinoma in situ in the vaginal cuff removed with the uterus. The pathologist must ascertain that the line of excision completely excludes such a lesion from the remainder of the vagina. Three of our patients with subsequent carcinoma of the vaginal vault were found to have had involvement of the vaginal cuff with carcinoma in situ which was overlooked at the time of vaginal hysterectomy. In 2 patients with carcinoma in the vault, no evidence of extension was present in the vaginal cuff of the surgical specimen. Others<sup>7, 18, 20, 21</sup> also have reported subsequent invasive carcinoma of the upper part of the vagina. Carter and co-workers postulated that "seeding" from the cervix or multiple independent foci of cancer might explain the appearance of vaginal carcinoma in a patient who apparently had received adequate treatment for the lesion of the cervix. The second explanation might be applicable in one of our cases in which simultaneous and multiple preinvasive carcinomas were present on the cervix, vagina, and vulva.

Only a few of the various methods of treatment employed during the years can be defended on the basis of present concepts of carcinoma in situ. Although it is true that simple office cautery or removal of a polyp has produced acceptable results in 14 cases in which it was employed, these results must be considered fortuitous, for the same procedures in many more cases left residual malignant lesions which were demonstrable in the excised uterus. The other extreme in therapy is radical hysterectomy or even simple hysterectomy combined with oophorectomy in the young woman. There seems to be no justification for employment of an operation more extensive than necessary to effect certain eradication of carcinoma in situ of the cervix.



Irradiation has a limited role in the treatment of carcinoma in situ. Its obvious disadvantage is the fact that the histologic evidence of a malignant neoplasm is usually obtained from a punch biopsy and therefore affords no absolute proof that the carcinoma is not invasive. The application of radium in a dose of approximately 3,000 mg. hr. has apparently controlled the malignant lesion in the several patients for whom operation was contraindicated, however. External irradiation does not serve a useful purpose and is no longer employed.

It is axiomatic that a lesion which is noninvasive should be controlled by removal of all involved tissue, and there is little dispute of the fact that this objective can be accomplished by hysterectomy and excision of the upper part of the vagina. Nevertheless, there is justification for an attempt, in some cases, to eradicate the cancer by a more conservative procedure such as conization.<sup>22, 23</sup> Rather specific criteria should be met, however, before it is decided to attempt preservation of the uterus. The patient should be in the childbearing age, preferably less than 30 or 35 years old, and should manifest a desire for pregnancy. The decision to accept the risk involved should be made by her and her husband only after the nature of carcinoma in situ has been explained to them as lucidly as possible. They should thoroughly understand that periodic postoperative smears are essential, and for this reason absence of a geographic barrier to follow-up examination is important. Finally, both gynecologist and pathologist must be as certain as possible that the carcinoma is noninvasive and that it is entirely circumscribed by the incision in the cervix. In all probability these criteria have not been fulfilled in some of the earlier cases in this series, and likewise conservative treatment would have been appropriate for some of the young women who underwent hysterectomy. To date evidence of persistence of carcinoma has not been found in any cervix treated by conization. The experience of Ayre and others,<sup>22</sup> however, indicates that the accumulation of a sufficient number of such cases will be followed by the detection, in at least a few, of residual cancer.

Management of the pregnant patient with carcinoma in situ remains more debatable than treatment of the patient who is not pregnant. The question of recognition of preinvasive carcinoma in the cervix during pregnancy is less hotly contested than it once was, and most pathologists agree that true, non-reversible neoplasia can and does occur during pregnancy. It is apparent that definitive treatment has been the rule rather than the exception in our small series of 14 patients, and this can be defended on the basis that it is consistent with the handling of the same problem in the nonpregnant patient. If a conservative attitude is to be adopted toward carcinoma in situ merely because it occurs during the course of gestation, the safeguards mentioned for conservative treatment of the nonpregnant patient should apply. Although multiple biopsies of preinvasive cancer do not place the pregnant woman in jeopardy,<sup>19</sup> the hazard of overlooking invasive cancer is ever present. One may argue that the long life history of carcinoma in situ justifies an expectant attitude toward the lesion during pregnancy, and the favorable outcome will prove this assumption to be correct in the majority of cases. Such cases as those of Te Linde and co-workers,<sup>21</sup> Taylor,<sup>24</sup> Laird,<sup>25</sup> Bryant,<sup>26</sup> and Carson and Gall<sup>20</sup> underscore the fact, however, that rapid progression from a Stage 0 to a Stage I lesion can occur or that a Stage I lesion might be missed by inadequate sampling.

The importance of meticulous re-examination after treatment cannot be overemphasized. Cytologic smears from the vaginal vault or from the cervix, if it remains, are essential.<sup>27</sup> Our experience is too limited to support any



statement regarding the desirable length of follow-up, but it is highly probable that incomplete removal of any carcinoma in situ will be reflected by a positive smear at the first follow-up examination.<sup>21, 22</sup> Conversely, repeatedly negative smears over a period of 2 or 3 years should offer adequate proof that the lesion has been eradicated.

### Summary and Conclusions

A total of 842 cases of carcinoma in situ of the cervix diagnosed and treated at the Mayo Clinic prior to Jan. 1, 1958, have been reviewed. Examination of a cytologic smear from the cervix played a definitive role in the detection of the malignant lesion in 363 cases. Our data indicate that the patient's symptoms and the appearance of the cervix offer unreliable evidence of the presence of a preinvasive malignant lesion.

Hysterectomy (vaginal, total abdominal, or Wertheim) was employed in 747 cases (88.7 per cent), but there are also specific indications for the therapeutic use of conization or radium.

The potential curability of carcinoma in situ depends on the certain demonstration that the lesion is noninvasive and that it does not extend beyond the vaginal or cervical incision.

Follow-up data for at least 2 years are available on 561 (96.0 per cent of the cases treated before 1956); 521 (92.9 per cent) of the traced patients are presumed to be free of cancer. Two hundred ninety-five (52.5 per cent) are well 5 years or more later. Thirty-four (6.1 per cent) are dead from unrelated disease. Six patients are known to have had subsequent carcinoma of the vaginal vault, and one of these is dead. One patient died in the immediate postoperative period.

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## THE APPLICATION OF CYTOLOGY TO A COMMUNITY UTERINE CANCER DETECTION PROGRAM

### Results and Experiences of Eleven Years' Operation

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PAPANICOLAOU<sup>1</sup> recognized cancer cells in smears from women with uterine malignancies in 1928, but his techniques were not widely accepted until after 1941 when he and Traut<sup>2</sup> showed that the vaginal smear technique "yields a high percentage of correct diagnoses when checked by tissue biopsies." Other investigators<sup>3-5</sup> saw the diagnostic possibilities of the method and undertook systematic studies of routine vaginal smears; their findings corroborated Papanicolaou's claims as to the value of the vaginal smear in the detection of cancer. This has been well established by numerous additional reports.<sup>6-12</sup>

Based on these early observations, conducted principally in hospitals and clinics, some workers<sup>13-17</sup> foresaw that the vaginal smear could be used to screen large numbers of the female population for uterine cancer. In 1947, the Academy of Medicine of Toledo and Lucas County organized a community uterine cancer detection program which used the vaginal smear techniques, and made this type of screening service available to the entire female population of the Toledo area.

Seven important principles formed the basis for the establishment of this program. These principles are vital to the successful organization of any large community uterine cancer detection program and are summarized in the following report.

1. *Enlist the Aid of the Pathologist.*—Cytology is different from histopathology and requires special study. The pathologist can best educate himself in this discipline by preparing smears from patients who are to have biopsies of the cervix and/or endometrium and comparing the individual cells with those seen in tissue sections. This should be supplemented by study of the illustrated literature on cytology, by examination of study slide sets, by group meetings, and by postgraduate studies.

2. *Use Cytotechnologists for Screening.*—Good cytotechnologists are indispensable to any large program. After 6 to 12 months of training they become exceedingly proficient in recognizing abnormal cells and can safely perform initial screening of slides. All abnormal or equivocal smears should be seen by the cytologist or pathologist.

3. *Utilize Practicing Physicians in the Program.*—The clinicians must first be convinced of the value of the program and educated in the methods and

limitations of the procedure. They must learn how to obtain material and make smears. The necessity of making a simultaneous pelvic examination should be emphasized. Limitations of the method should be pointed out: suspicious lesions should be biopsied regardless of smear findings; no therapy should be instituted without a confirming biopsy.

With the aid of the clinician and the pathologist the program quickly becomes established. In Toledo the work is being done by practicing physicians in their own offices, a feature of great importance if large segments of the population are to receive the benefit of cancer detection procedures.

*4. Tell the Patient About the Program.*—Educate the women of the community in the value of the examination. Properly informed patients assure the growth and success of the program. They must understand why cytology makes for early diagnosis of cancer and realize the importance of returning for regularly repeated examinations even though no symptoms are present. This can be accomplished by doctor-patient conferences, pamphlets, talks by physicians to women's organizations, illustrative movies, and radio and television publicity.

*5. Provide Continuity of Examination.*—Repeated cytologic and pelvic examinations at 6 to 12 month intervals are at present the only effective means of providing adequate diagnostic protection. The patient should enroll in the program when at most 25 to 30 years of age and continue throughout her lifetime.

Such continuity has been achieved in the Toledo Program through a Cancer Continuity Control Center established and operated by the Academy of Medicine of Toledo and Lucas County. This center functions in the operation of the Toledo Community Uterine Cancer Detection Program as follows:

The patient is seen in the doctor's office where a pelvic examination is made and cytologic smears are prepared.

At this time a request form, put together in triplicate, is filled out, and, along with the smears, is sent to a pathologist who makes a report of the findings. The three copies are then distributed: the first copy goes to the doctor, who in turn contacts the patient and recommends treatment if necessary; the second copy remains in the pathology laboratory; the third copy, a card, is sent to the Academy of Medicine Cancer Continuity Control Center where it is placed in a monthly follow-up file.

At the end of 6 or 12 months the card is pulled out and two notices are sent to the doctor. One tells him that his patient is due to report for another pelvic examination and smear. The other notice is for the patient: it is sent to her by her doctor; on it he sets the date for her next examination and asks her to follow a few simple routines before she reports.

The patient returns to the doctor and the cycle is thus completed. As long as the chain remains unbroken the patient will receive regular periodic examinations throughout her lifetime.

So far as we can determine, Toledo was the first to incorporate continuity of examination into a community-wide cancer detection program.<sup>18</sup> The importance of this feature cannot be overemphasized. Single examination surveys detect malignancies in an individual at any one given time, but they do not offer lifetime protection against being surprised by late uterine cancer.

*6. Preserve the Doctor-Patient Relationship.*—To succeed on a large scale, community programs must preserve the doctor-patient relationship. This is easily accomplished when smears and pelvic examinations are made in the office of the patient's physician and when communications from a Continuity Control Center are sent only to the doctor, never directly to the patient.



7. *Make the Program Self-Supporting.*—The program must be essentially self-supporting if growth and continuity of examination are contemplated. The Toledo plan essentially finances itself since the women who are able pay a nominal fee for the smear examination. Indigent patients are examined free both by the practicing physician and by the pathologist. The subsidization of the Cancer Continuity Control Center by the American Cancer Society constitutes the only non-self-supporting aspect of the program.

The results of the program during the first 11 years of operation have been gratifying. More than 110,000 pelvic and cytologic examinations have been made on approximately 47,000 women. Many of the women, once enrolled, return regularly for repeated examinations at 6 month or yearly intervals. Approximately 600 practicing physicians have participated in the program during the 11 year period.

Histologically proved uterine cancer has been found in more than 430 women. Of these, approximately 275 had some signs or symptoms of neoplasm; the smears provided only corroborative evidence in these clinically suspected cases. More than 155 women, however, had no evidence of cancer; these occult malignancies were detected primarily by means of smears. Follow-up studies<sup>19</sup> on our material indicate that in occult uterine cancer, usually an early lesion, a 91 per cent 5 year cure rate may be expected, as compared with a 38 per cent 5 year cure rate for women with suspected neoplasms. This represents more than a twofold increase in the 5 year cure rate of the presymptomatic over the symptomatic group.

The Toledo Program has not only produced increased cure rates during its 11 years of operation, but has also made possible the accumulation of material with great research potential. Some of the women enrolled in the program have had repeated pelvic and cytologic examinations over a period of from one to 11 years and have developed malignancies during that time. The microscopic preparations and clinical findings of these women are available for review; study of these data should reveal many interesting facts about human uterine carcinogenesis.

### Summary

The mode of operation of the Toledo Community Uterine Cancer Detection Program, established in 1947, is described. Seven important principles formed the basis for the program, among which three steps are unique, so far as we know, for a community operation.

1. *Continuity of Examination.*—Once a woman is enrolled in the program, she receives repeated pelvic and cytologic examinations at 6 to 12 month intervals throughout her lifetime.

2. *Self-Supporting Program.*—The program is essentially self-supporting; those who are able pay fees. Indigents are examined free both by physicians and pathologists.

3. *Utilization of Practicing Physicians.*—The work is being done by practicing physicians in their own offices.

The results of the first 11 years' operation of the program are outlined.

1. More than 110,000 pelvic and cytologic examinations have been made on approximately 47,000 women.

2. Histologically proved uterine cancer has been detected in more than 430 women. Of these, 275 had clinically suspected cancers while more than 155 had clinically occult neoplasms which were detected primarily by means of smears.

3. Women with occult uterine cancer had a 5 year cure rate of 91 per cent as compared with 38 per cent for those with suspected neoplasms.

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## EPITHELIAL CHANGES PRECEDING SPINAL-CELL CARCINOMA OF THE CERVIX UTERI

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THE picture of basal-cell hyperactivity or hyperplasia has been adequately described and is an accepted entity where intraepithelial carcinoma has been carefully and systematically studied. Similarly, the histologic findings in preinvasive carcinoma or carcinoma in situ of the cervix have been well documented. The criteria required to justify the diagnosis of the latter involve complete loss of the normal stratification; i.e., the elongated basal cells and the round or ovoid transitional cells have demonstrated overactivity by replacing or eliminating the formation of the superficial spinal or prickle cells. This seems to be the logical course of events in the usual basal and transitional type of carcinoma, i.e., Broders Grades II, III, and IV. The preinvasive changes in spinal-cell carcinoma, however, appear to present a different picture from that described above. This is certainly true of skin, where Bowen's disease shows a very different appearance from the carcinoma in situ described in the cervix.

Our attempt to determine whether there is such a difference was approached in three ways: (1) cases diagnosed as spinal-cell carcinoma, i.e., Broders Grade I, were reviewed with the idea of studying the epithelium adjacent to the invasive lesion; (2) cases diagnosed as "spinal-cell hyperactivity" or "spinal-cell atypia" were followed carefully as to the development of invasive disease; (3) cases diagnosed as intraepithelial carcinoma were rechecked as to the type of cell showing the most striking changes.

The features which are felt to be suspicious of spinal-cell atypia or hyperactivity are: (1) Cellular abnormalities (an example of which is shown in Fig. 16): There is essentially normal stratification, although the epithelium is often thickened with elongated rete pegs. The basal layer is intact with little acanthosis. Occasionally, there is some hyperplasia of basal or transitional zones. The spinal layer is about normal in thickness but in this layer are seen the abnormal cells. These consist primarily of large, hyperchromatic nuclei, vacuolization of the nuclei (simulating Paget's cells), and clumping of the nuclei with production of multinucleated epidermal cells. (2) Intraepithelial keratinization (an example of which is shown in Fig. 4): Pegs of epithelium extend down from the basal layer with central keratinization, and

pearl formation is noted in these pegs. This resembles individual cell keratinization, a feature of Bowen's disease. (3) Squamous papilloma (an example of which is shown in Fig. 12): Although papilloma is essentially a benign disease, there are many variations seen on the skin. The senile keratosis shows marked papillomatosis, hyperkeratosis, and some downward proliferation of the rete. This condition is felt to be a definite premalignant disease in the skin, and has been similarly noted in the cervix. Allusion has been made to some of these changes and their malignant possibilities.

Kistner and Hertig<sup>1</sup> have reported on cases of papillomatous lesions of the cervix and have called attention to the squamous papilloma as being more commonly a precursor of carcinoma than other varieties of papillomas. Greene and Peckham<sup>2</sup> have recorded a case in which the evidence of pearl formation in a cervical papilloma was mistakenly interpreted as a benign condition, yet the patient developed invasive cancer within the year. Such microscopic observations are not unusual in other areas where squamous epithelium is the surface covering. Fisher<sup>3</sup> has discussed intraepithelial carcinoma in general and has shown photomicrographs of characteristic changes in other areas. One of his cases, an esophageal lesion, demonstrated microscopic changes similar to those noted in the cases reported here, namely, irregular clumping of the nuclear material, vacuolization in the nuclei, abnormal mitosis, and occasional keratinization in the individual cell within the epithelium. These changes, of course, have been described frequently in cases of Bowen's disease of the skin. Instances of this condition of the vulva have been described by van Dyck Knight.<sup>4</sup> Furthermore, the unusual intraepithelial pearl formation has created confusion in the designation of vulvar lesions, as shown by Salzstein, Woodruff, and Novak<sup>5</sup> in Fig. 4 of gross carcinoma of the vulva of condylomatous type. In spite of definite invasion into the adjacent structures and pubic bone, the microscopic picture in this case was far from diagnostic of malignant change. Various observers disagreed on the designation but none would positively diagnose carcinoma on the evidence present. The patient died within one year of the initial operation. These reports emphasize the difficulty in distinguishing benign overgrowth of the squamous epithelium, such as that seen in papillomatous lesions, from the well-differentiated carcinoma. Furthermore, the reports of Bowen's disease, which is generally conceded to be a type of intraepithelial carcinoma, indicate that, at least on the common squamous surfaces, the appearance is very different from that generally associated with the use of the various terms for preinvasive disease of the cervix. In other words, the impetus for the anaplasia change in the epithelial cell, wherever it may have been initiated, seems to demonstrate its effect in the more mature cell.

Of interest is the occasional finding of hyperactivity or, better, atypical changes in all layers, so that the diagnosis cannot be limited to one zone. This characteristic, of course, has been apparent in the work on invasive cancer and has been recorded by many observers. Martzloff,<sup>6</sup> in 1923 divided carcinoma of the cervix into three groups depending on the maturity of the cell comprising the malignant tissue, i.e., basal, transitional, or spinal. This



division was initiated in order that a better decision might be made as to the most effective therapy for the individual case, since it was felt that the more immature the cell, the more sensitive this cell would be to radiation therapy. By the same token, the more mature cell was less affected, and such a case was felt to be better treated with surgery. Unfortunately, as Martzloff later reported, it is not uncommon to find that the type of cell noted in the biopsy did not correspond to the predominant cell in the removed specimen. Furthermore, there were frequent variations from one area in a tumor to another. In other words, there are few "pure" malignant neoplasms made up solely of one type of cell. Fig. 9 demonstrates such a mixed type of change within the epithelium, basal-cell hyperactivity on the left and abnormality in the spinal-cell layer on the right.

As in all microscopic patterns, there are pitfalls to be considered. Not uncommonly, epithelium is cut tangentially, particularly in the biopsy specimen (Fig. 1) so that there is apparent increased thickness of all layers and the spinal cells may appear to be in the basal layer. This might be confused with the well-differentiated type of intraepithelial pearllike formation. This is more commonly seen in the papillomatous type of lesion which is more easily recognized because of the hyperkeratosis. The degenerative changes which may be seen especially in cervixes which are badly infected or which have been traumatized by surgery or irradiation offer more difficulty in differentiation (Fig. 2). The late Emil Novak<sup>7</sup> felt that most of the changes in the well-differentiated cells on the surface were degenerative. Often this degeneration can be recognized by the disorganization of the nuclear material and the absence of real mitotic activity. It is often necessary, however, in cases of tangentially cut or badly traumatized or infected tissue, to request further studies. Finally, epidermization may present a confusing picture (Fig. 3). The gland that is completely occluded by the "invasion" of the surface squamous epithelium may demonstrate apparent pearl formation beneath the surface epithelium. Tangential cutting may further accentuate this abnormality. Reimbedding and/or further section of the tissue may clear up this confusion. If necessary, further tissue should be obtained.

### Case Presentations

CASE 1.—S. B. (J.H.H. No. 651440), a 43-year-old Negro woman, para 1-3-4-1, was first seen in the gynecologic outpatient department in November, 1953, with the chief complaint of postcoital bleeding of 2 months' duration and a slight bloody vaginal discharge for one week. Pelvic examination at that time disclosed a hypertrophied, firm, somewhat irregular cervix with transverse lacerations. A cervical biopsy (Fig. 4) showed a thickened epithelium with diffuse inflammatory infiltrate involving the epithelial layer. The basal layer was made up of a single row of elongated spindle cells. The spinal cells were generally uniform although acanthosis was present and occasional abnormal nuclei were seen. There was, however, a definite tendency to the formation of pearls in the epithelium. Unfortunately, the patient did not return until 2 years later, November, 1955, at which time the cervix was completely replaced by a cauliflower growth with parametrial extension almost to the left lateral pelvic wall. Cervical biopsy at this time showed invasive carcinoma. Again, the pattern was that of the well-differentiated squamous-cell tumor with a tendency to pearl formation. Mitoses were common in the basal layer but only a single layer or two of basal

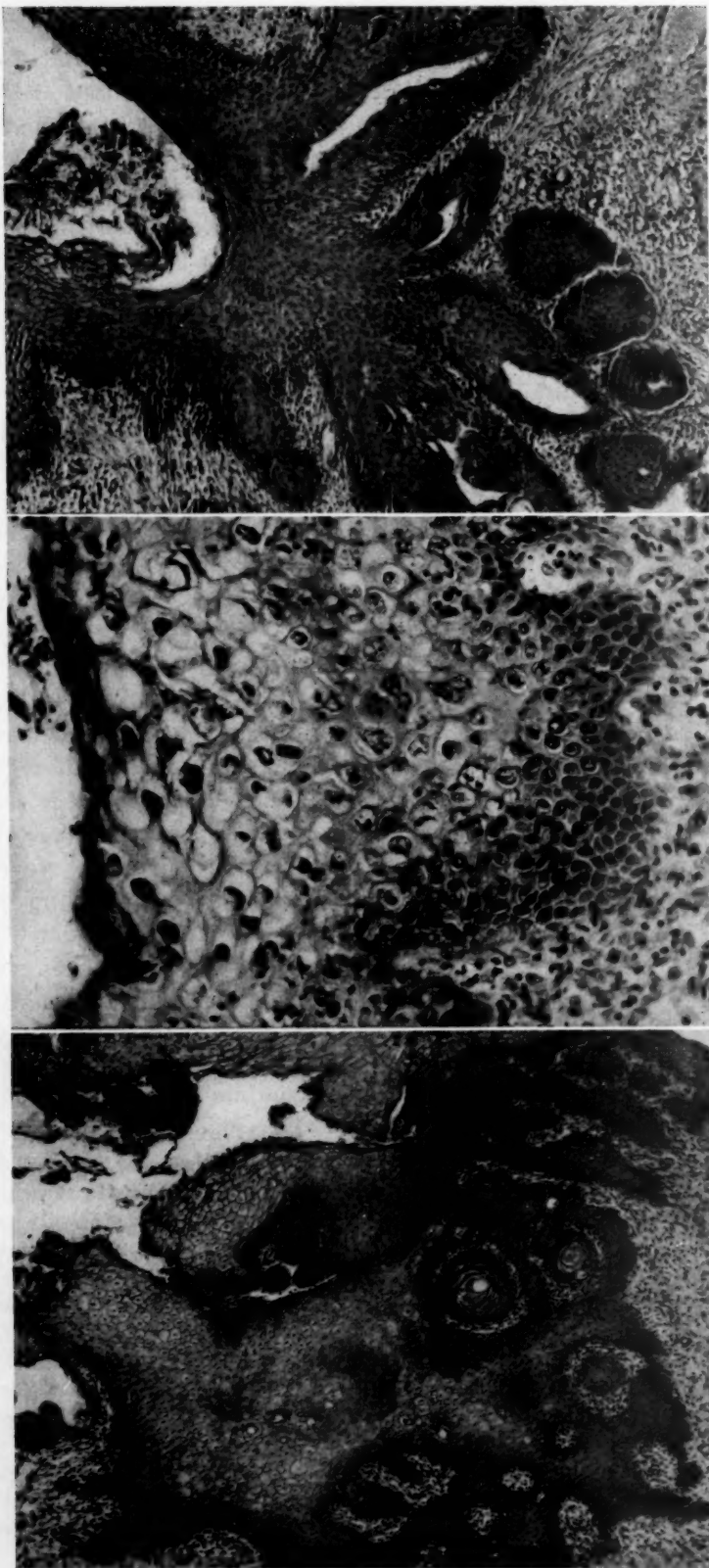


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Tangential cut of epithelium showing pearl formation and apparent marked thickening of epithelium. Benign change.  
Fig. 2.—Degenerative changes showing breakdown of the nuclei with inflammatory infiltrate in the epithelium.  
Fig. 3.—Epidermization showing well-differentiated epithelium involving the glands and producing picture simulating pearl formation.

cells were present and the proliferation was apparent primarily among the well-differentiated cells (Fig. 5). The patient received full irradiation therapy and shows no evidence of recurrence to date.

CASE 2.—F. A. (J.H.H. No. 405452), a 39-year-old Negro woman, para 1-0-0-1, was first seen in the gynecologic clinic in November, 1946, for menometrorrhagia of 4 months' duration. Pelvic examination showed an elongated cervix with transverse lacerations and a hypertrophied anterior lip. A curettage and cervical biopsy were performed. The cervical biopsy showed a thickened epithelium with many mitotic figures and areas showing cells with large nuclei, prominent nucleoli, and a large amount of clear cytoplasm. These cells extended into the intermediate zone of the epithelium. The upper spinal zone showed marked distortion of the cells with much vacuolization and clumping of nuclear material. The basal

Fig. 4.

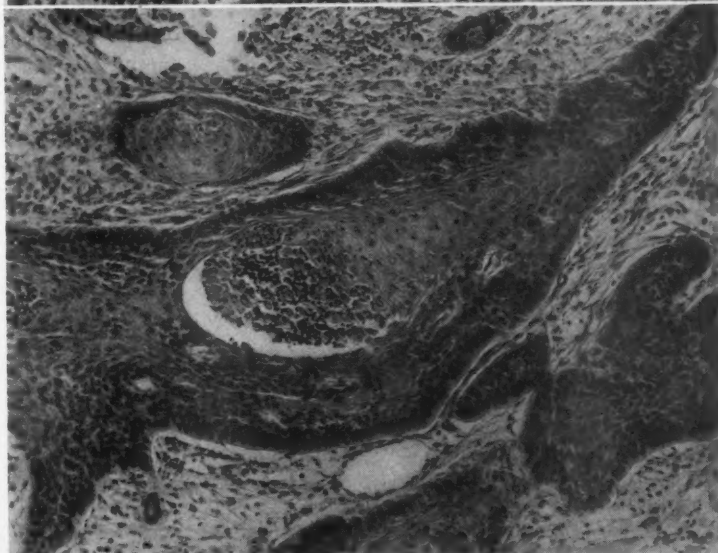
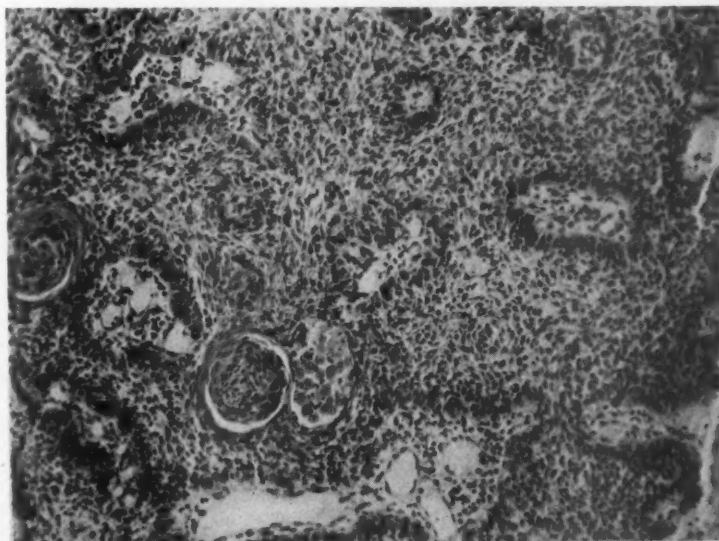


Fig. 5.

Fig. 4.—Case 1, showing tendency to intraepithelial pearl formation. Spinal-cell layer is relatively intact.

Fig. 5.—Case 1. Biopsy 2 years after Fig. 4 showing invasive cancer of the well-differentiated type.

layer was intact but distorted by abnormal nuclei. These changes were considered typical of marked spinal cell hyperactivity (Fig. 6). The patient did not return to the clinic until May, 1950, at which time she was admitted to the hospital for menorrhagia. Examination showed only a small ulceration on the ectocervix. Cervical biopsy showed much the same epithelial changes as noted in 1946 but in addition there were long epithelial projections into

Fig. 6.

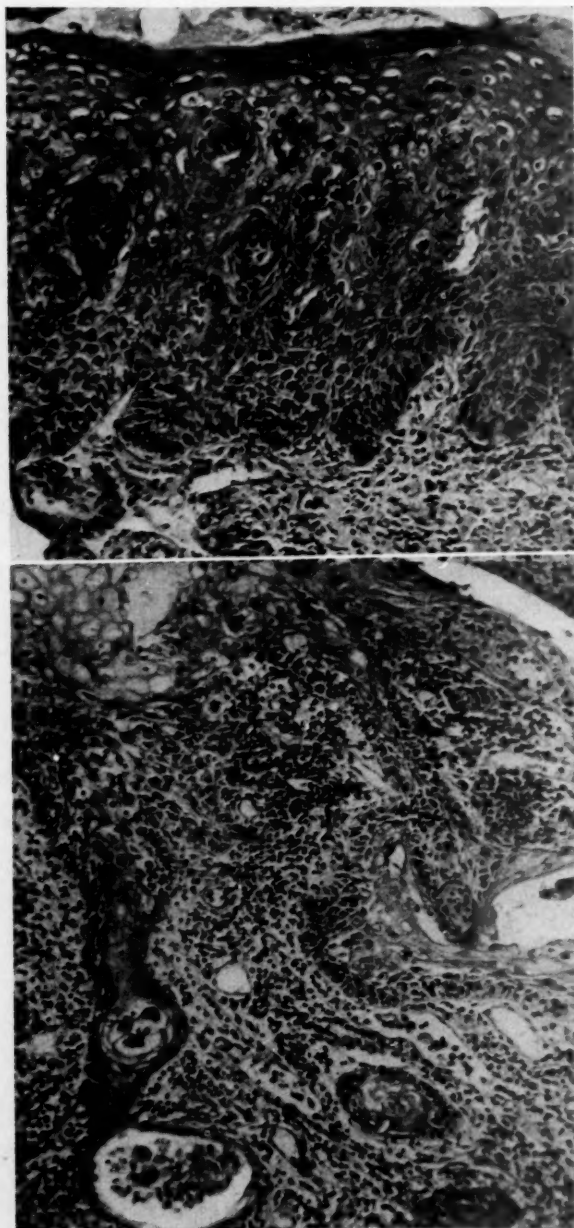


Fig. 7.

Fig. 6.—Case 2. Biopsy showing stratification of normal type but marked cellular changes throughout.

Fig. 7.—Case 2. Biopsy 4 years after Fig. 6 showing invasive cancer of the well-differentiated type.



the underlying stroma with keratinization and pearl formation, typical of invasive spinal-cell carcinoma (Fig. 7). The patient was treated with full irradiation therapy but died in 1954 of cardiac arrest while being operated on for a ruptured appendix. Autopsy disclosed no evidence of residual tumor.

CASE 3.—G. F. (J.H.H. No. 206754), a 31-year-old Negro woman, para 0, was first seen in the gynecologic clinic in August, 1940, with a clinical diagnosis of chronic salpingitis. Pelvic examination at that time showed a small area of cervical erosion but biopsy was not obtained. The patient was next seen in August, 1952, at the age of 43, complaining of lower abdominal pain. She was found to have a large myoma of the uterus and was admitted to the hospital for hysterectomy. Pelvic examination on admission showed minimal eversion of the external cervical os but the cervix was otherwise clean and normal in appearance. A pre-operative biopsy showed surface epithelial changes of both basal- and spinal-cell hyperactivity as well as intraepithelial carcinoma with gland involvement. Although there was much obvious basal-cell hyperplasia in some areas, there was also a tendency to more differentiation



Fig. 8.

Fig. 8.—Case 3 showing basal-cell hyperactivity on the surface but changes in the glands are better differentiated.

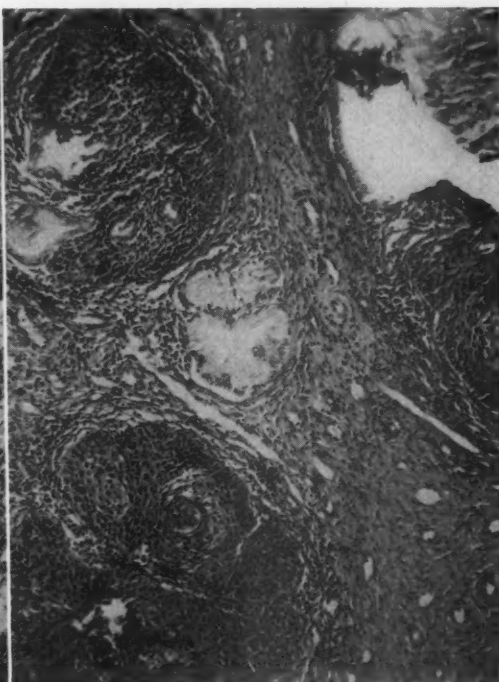


Fig. 9.

Fig. 9.—Case 3. Section from hysterectomy specimen showing gland involvement and both basal- and spinal-cell changes with attempt at pearl formation.

and actual pearl formation in some areas (Fig. 8). A modified Wertheim hysterectomy was performed and the gross specimen showed intraepithelial carcinoma with glandular involvement and pearl formation. Both basal- and spinal-cell changes were noted (Fig. 9) as is not uncommon in advanced cervical carcinoma. The patient has remained well since the operation.

CASE 4.—L. C. (J.H.H. No. 545522), a 48-year-old Negro woman, para 1-0-1-1, was first seen in the gynecologic clinic in August, 1950, having been referred by her local physician for a cervical biopsy because of the finding of mild cervical eversion on routine pelvic examination. The only abnormal menstrual history was the occurrence of vaginal spotting

for 2 or 3 days at the cessation of each menstrual period for the last 6 months. Cervical biopsy at this time showed probable intraepithelial carcinoma, showing basal- and spinal-cell hyperplasia with glandular involvement. On Aug. 10, 1950, examination revealed a granular

Fig. 10.

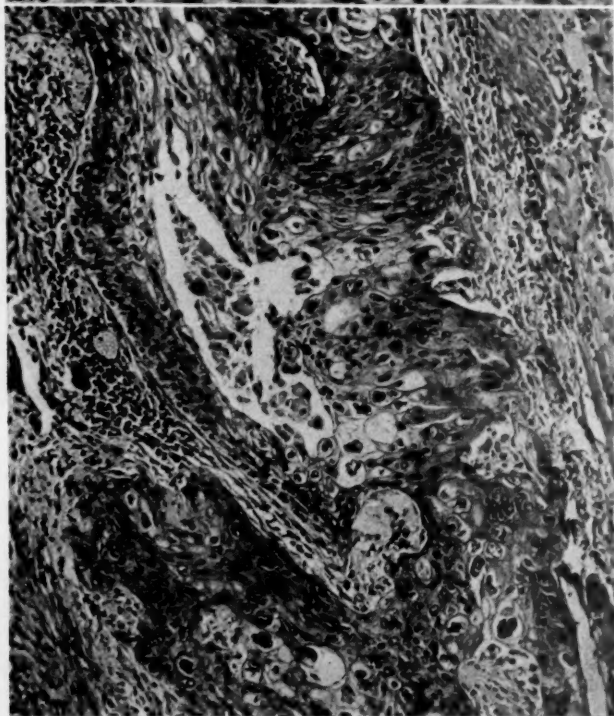
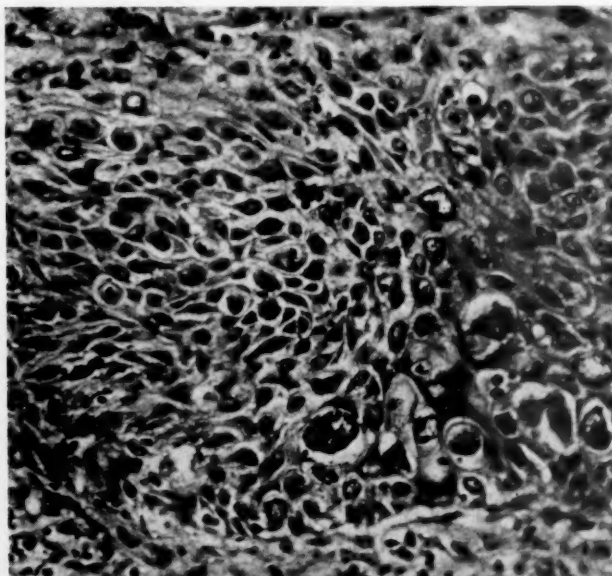


Fig. 11.

Fig. 10.—Case 4, showing epithelial changes, some of which appear degenerative but others anaplastic.

Fig. 11.—Case 4. Invasive carcinoma in hysterectomy specimen showing well-differentiated type of cancer.

area on the posterior lip of the cervix. On biopsy (Fig. 10), the changes in the surface epithelium were striking, with numerous mitoses, clumped and vacuolated nuclei. The basal layer was eliminated as a definite zone in many areas. Because of the microscopic findings of only very minimal stromal invasion, the patient was treated by a modified Wertheim hysterectomy. The gross specimen showed typical spinal-cell carcinoma with early stromal invasion (Fig. 11). The patient has remained well with no evidence of recurrence.

CASE 5.—V. C. (J.H.H. No. 289881), a 25-year-old Negro woman, para 2-0-0-2, was first seen in April, 1954, in the gynecologic clinic, where she was treated with antibiotics for subacute salpingitis. At that time, the cervix showed fairly marked erosion and a biopsy showed microscopic papilloma formation. There was acanthosis with a thick layer of hyperkeratosis on the surface associated with the papillomatosis. In the thickened proliferative spinal layer of the epithelium, abnormal nuclei were frequent, and in these areas the basal layer was disrupted (Fig. 12). A sharp conization of the cervix was carried out which confirmed the diagnosis of intraepithelial carcinoma, spinal-cell type, with glandular involve-

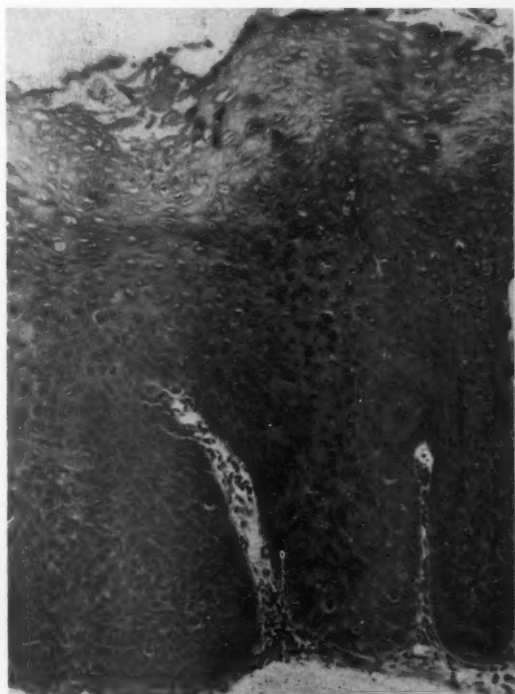


Fig. 12.

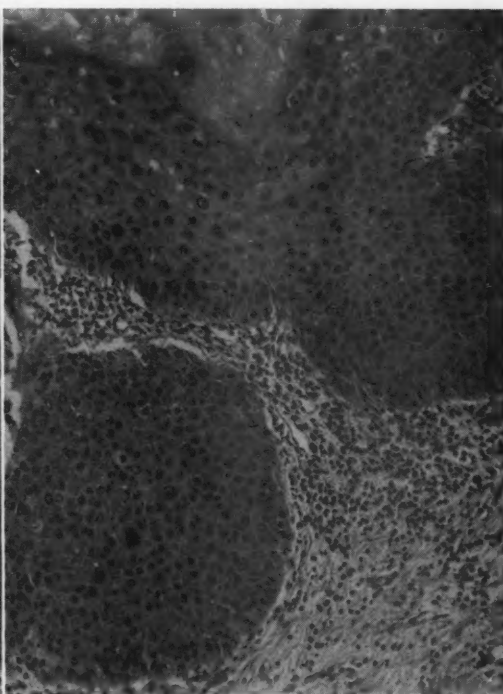


Fig. 13.

Fig. 12.—Case 5. Papilloma-type picture with hyperkeratosis and acanthosis. Cellular changes noted in central peg.

Fig. 13.—Case 5. Section from hysterectomy specimen showing hyperkeratosis with marked cellular changes in spinal-cell layer.

ment (Fig. 13). A modified Wertheim hysterectomy was performed and the gross specimen showed pathologic changes similar to those described above. The patient has remained well with no evidence of recurrence.

CASE 6.—M. W. (J.H.H. No. 449106), a 23-year-old Negro woman, para 1-0-0-1, was first seen in the gynecologic clinic in February, 1950, for menorrhagia. Pelvic examination revealed a normal-appearing cervix and the patient was thought to have chronic salpingitis. The patient was not seen again until November, 1957, at which time she was again thought to have salpingitis. The cervix now showed marked erosion and was somewhat hypertrophied. There was a sanguineous vaginal discharge. Cervical biopsy disclosed marked spinal-cell



hyperactivity. The patient was scheduled for a curettage to rule out the possibility of pelvic tuberculosis, as she was known to have a tuberculous skin ulcer of the right leg which was under therapy. The curettings revealed normal endometrium but the cervical biopsy showed spinal-cell intraepithelial carcinoma. A modified Wertheim hysterectomy was performed and the gross specimen contained spinal-cell carcinoma in the surface epithelium with some glandular involvement (Fig. 14). The postoperative course was uneventful and the patient was recently discharged from the hospital.

CASE 7.—G. C., a 34-year-old white woman, para 1-0-0-1, was seen Sept. 30, 1957, complaining of infertility. She had had irregular intervals varying from 14 to 30 days and two to three episodes of postcoital bleeding. The patient had had "gonococcal" arthritis in 1945. She had had one full-term pregnancy sixteen years before by her first husband. Results of examination were essentially normal except for the pelvis. The cervix was lacerated with several "white" patches on the portio. The fundus was in retroposition, normal in size, and free. The vaginal smear showed many white blood cells and an occasional trichomonad. The



Fig. 14.—Case 6. Section from hysterectomy specimen showing cellular changes on surface with glandular involvement (anaplasia not marked in glands). Biopsy showed similar changes.

patient was treated for *Trichomonas* infection and was admitted for infertility studies on Oct. 31, 1957. The Rubin test was successful. The endometrium was secretory. The biopsy showed marked cellular irregularity in the more well-differentiated areas of the spinal-cell zone with similar changes in the glands (Fig. 15). The biopsy was repeated on Nov. 11, 1957, with similar results and, on Nov. 16, 1957, a total hysterectomy was performed with excision of 2 to 3 cm. of vaginal cuff and adjacent paracervical tissue. Normal left adnexa were left in. There was extreme change in the surface epithelium with large hyperchromatic and vacuolated nuclei. The basal-cell layer was distorted and mitoses were frequent. There was glandular involvement showing similar changes (Fig. 16).

#### Comment

The study of epidermoid carcinoma has demonstrated to the satisfaction of most observers that, in the majority of cases, there is a preinvasive stage of



the disease. This stage may be present for variable periods of time before actual breakthrough into the underlying tissue takes place. Petersen<sup>8</sup> has demonstrated the time lag between preinvasive and invasive cancer in the follow-up of 127 untreated cases of carcinoma in situ at the Radium Center in Copenhagen from 1930 to 1950. The microscopic pictures of these preinvasive epithelial lesions may vary considerably depending on the region of the body which is under study. For example, in 1912 Bowen<sup>9</sup> described the disease which now bears his name. This lesion of the skin is quite different from the common variety of carcinoma in situ of the cervix described by Galvin and Te Linde.<sup>10</sup> The difference between these lesions seems to lie in the layer of stratified epithelium in which the major cellular changes can be demonstrated.

Fig. 15.

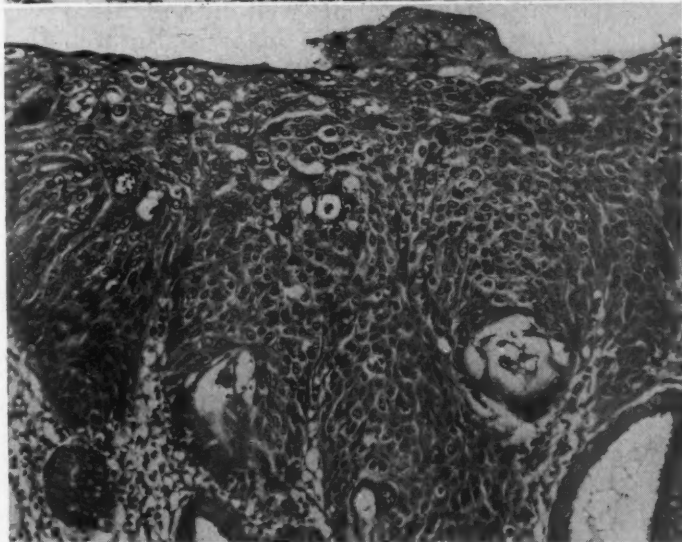
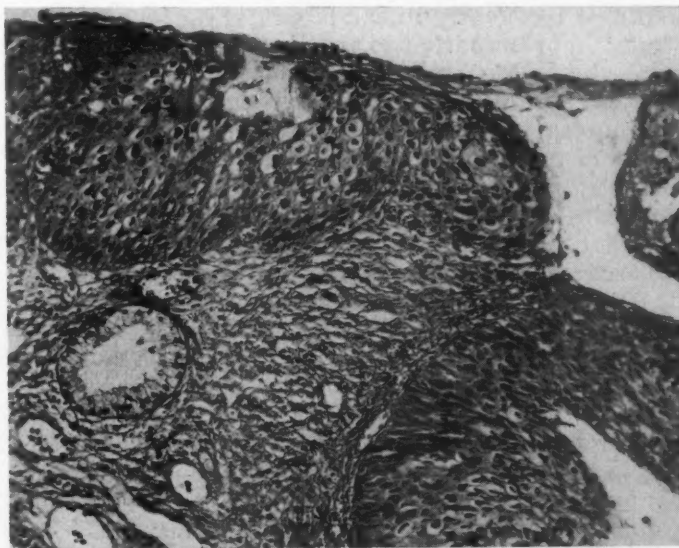


Fig. 16.

Fig. 15.—Case 7, showing extensive cellular changes in surface epithelium and in that involving the glands.

Fig. 16.—Case 7. Section from hysterectomy specimen showing extensive cellular changes as seen in Fig. 15.

Whereas the common variety of carcinoma in situ of the cervix shows microscopically complete loss of the normal stratification due to extreme overactivity of the basal and transitional zones and a loss of the spinal-cell layer, there is an occasional case in which the major changes seem to be present in the superficial zone. In view of these occasional findings, the authors made an effort to follow these cases to determine whether or not the well-differentiated epidermoid carcinoma is not often preceded by anaplastic changes in the spinal-cell layer. The cases presented in this report are felt to strengthen the evidence for the premise that, although the impetus for the anaplastic tendencies in a cell may affect only the most immature basal cells, nevertheless, these cells may not demonstrate their malignant potentialities until they have progressed to varying degrees of maturity.

Cases demonstrating changes similar to those described in detail herein have been recognized frequently in the laboratory. It was felt wise, however, to choose the most representative examples to include in this initial report. As stated earlier, this subject was approached in three ways: (1) A study was made of the epithelium adjacent to the invasive cancer in cases diagnosed as spinal-cell carcinoma. An example of surface changes in a case of proved invasive cancer is demonstrated by the illustrations in Case 4. It must be stated, however, that basal-cell changes also may be seen in such cases since overactivity limited solely to a single differentiated zone is not very commonly seen in either hyperactivity or true cancer (Case 3). (2) A careful follow-up of all cases diagnosed as spinal-cell hyperactivity is being carried out. Although few of these have resulted in the development of true invasive cancer, the time has been too short to determine the final outcome in a majority of the patients. Surface and glandular changes of the type described in this report both in biopsy and gross specimens are exemplified by the illustrations in Cases 5, 6, and 7. (3) A review of cases diagnosed as atypical epithelium or hyperactivity disclosed many cases in which the anaplasia changes were noted in both spinal- and basal-cell layers. In some, the spinal-cell hyperplasia was the predominant abnormality, and in 2 of these, Cases 1 and 2, invasive carcinoma developed in succeeding years. The malignancy was histologically of the most matured or well-differentiated variety. These cases tend also to be further evidence in favor of the hypothesis suggested under section (1) in this paragraph, namely, that the surface changes adjacent to invasive spinal-cell carcinoma are primarily those of hyperactivity in the well-differentiated zone.

The three most striking features of the epithelial changes in this group of cases, characterized as spinal-cell hyperactivity of intraepithelial spinal-cell carcinoma, are as follows:

1. The squamous-cell papilloma with hyperactivity evidenced by hyperkeratosis, acanthosis, papillomatosis, and individual cell changes, such as nuclear clumping, vacuolization of abnormal nuclei, and enlarged cells with bizarre nuclei.
2. The tendency to intraepithelial keratinization or pearl formation. There are usually elongated rete pegs with the keratinizing layer extending down into the pegs or individual pearls appearing well beneath the surface layer. Such changes are of course seen in their most striking form in invasive spinal-cell carcinoma.
3. Proliferation of the stratified epithelium with hyperactivity seen in all zones. This represents, then, not a complete loss of stratification, but nevertheless demonstrates in all layers intraepithelial anaplasia by individual cell changes, such as mitosis and variations in size, shape, and staining qualities of the nuclei.

It should be reiterated that certain pitfalls must be recognized. Tangential cutting can produce the appearance of pearl development in the epithelium. Extensive epidermization is a common finding in the endocervix and again may lead to the false impression of overactivity. Degenerative changes due to infection and x-ray therapy produce remarkable alterations in nuclei and these may simulate the clumping of nuclear chromatin material resembling that seen in overactivity of the spinal cells. These changes obviously demand further study to prove their true nature.

### Conclusions

1. Preinvasive cancer of the cervix is a well-known entity and the usual microscopic picture has been accepted by most pathologists.
2. Certain evidences of overactivity in the epithelium do not always follow the usual lines, but seem to demonstrate anaplastic activity in the most superficial zones.
3. Seven cases are presented in this report to substantiate this thesis.
4. The various microscopic features which should be recognized as evidence of the hyperactivity in the spinal-cell zone are outlined.
5. Pitfalls in microscopic examination which may cause confusion with malignant alterations are described.

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## CARCINOMA METASTATIC TO THE UTERINE CERVIX

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CANCER which metastasizes to the uterus is rarely reported but is not infrequently encountered as an incidental finding at autopsy, usually in cases with generalized carcinomatosis of the peritoneum. In contrast, carcinoma metastatic to the uterine cervix is quite rare. No note of such an occurrence is found in general textbooks of pathology or gynecology<sup>1-5</sup> and few cases have been reported.

In a review of metastatic carcinoma of the uterus, Charache<sup>6</sup> found 59 reported cases, including 34 from the breast, 14 from the stomach, 3 from the lungs, 2 from the kidney, and one each from pleura, pancreas, liver and gall bladder. He made no specific notation of tumor in the cervix.

Williams<sup>7</sup> reported the case of a 32-year-old nulliparous woman with nausea, vomitings, weight loss, and weakness for 10 months. The only symptoms referable to the gynecologic system were mild dysmenorrhea and some increase in menstrual flow for 2 or 3 months. The cervix showed bleeding from the os and was firmly fixed, indurated, and "woody," but no ulceration was noted. Exploratory laparotomy showed a nodular mass high on the lesser curvature of the stomach and numerous tumor nodules on the peritoneal surface including the surface of the ovaries and fundus of the uterus. Microscopic sections from these sites and from the cervix all showed anaplastic adenocarcinoma with many signet cells. The final diagnosis was metastatic adenocarcinoma of the cervix from a primary gastric cancer. Autopsy examination was not performed, however.

Stein<sup>8</sup> reported a case of chronic lymphatic leukemia which presented as a neoplasm of the uterine cervix. The patient was a 57-year-old woman with vaginal bleeding and discharge for 1½ years and weight loss for 2 years. "On the basis of the vaginal examination carcinoma of the cervix was diagnosed with infiltration into the parametrium on both sides." Work-up in the hospital led to the diagnosis of chronic lymphatic leukemia. It was then considered that the lesion of the cervix could represent leukemic infiltrate. The cervix was large with small nodular excrescences on both lips, perhaps not as hard as one would expect in carcinoma of the cervix. Biopsy of the cervix showed a dense leukemic infiltrate in the connective tissue usually sparing the subepidermal zone but occasionally involving the epithelium.



Boysen, McCloskey, and Scheffey<sup>9</sup> reported the case of a 65-year-old woman with slight vaginal bleeding and lower abdominal pain for one week and anorexia, nausea, and weight loss for one year. Examination of the cervix showed an extensive necrotic tumor which involved both anterior and posterior vaginal walls. The fundus was enlarged; both adnexa were fixed and indurated. The clinical impression was squamous-cell carcinoma of the cervix, Grade IV, Stage III. Biopsy of the cervix was reported as anaplastic carcinoma (Grade IV). X-ray therapy was given. Autopsy examination showed primary carcinoma of the pancreas with metastases to the adrenals, lymph nodes, ovaries, broad ligaments, uterus, and cervix. These authors mention an additional case of metastatic carcinoma of the stomach reported by von Franque.

Reidenberg<sup>10</sup> reported upon a 46-year-old woman para iv, with vaginal bleeding, enlargement of the abdomen, backache, and anorexia for 2 months. Physical examination, including pelvic examination of the uterus, adnexa, and cervix showed no abnormalities. Biopsy of the cervix was reported as showing anaplastic carcinoma. Ascites developed and tumor cells were found in this fluid. X-rays were reported as demonstrating scirrhus carcinoma of the stomach. At laparotomy there was generalized abdominal carcinomatosis. Autopsy confirmed the primary carcinoma of the stomach with metastasis to the cervix.

Cruz<sup>11</sup> described the case of a 47-year-old woman admitted for hematuria who had had a radical mastectomy 5 years previously for mammary carcinoma. Previous workup for menorrhagia one year before showed a normal-appearing cervix; biopsy of the cervix and endometrium had been normal. At the present admission the cervix was hard but smooth. Biopsy of the cervix showed a well-circumscribed nodule in the deeper fibromuscular zone, not connected with the cervical epithelium. This tumor was considered to be metastatic and the comparison of tissue slides from the cervix with those from the breast revealed the identity of the two lesions. The patient was alive at the time of the report.

### Case Report

E. S., a 73-year-old white woman, was admitted for the first time to the Bronx Municipal Hospital Center in May, 1957, because of a lump in the breast for 3 years, diminished hearing and tinnitus in the left ear for 5 years, and "twisting" of the left side of the face for 2 to 3 years with excessive tearing of the left eye. For 6 months she has been unsteady on her feet and had intermittent tingling discomfort radiating from the left upper gum area to the left cheek with pain around the left eye.

On physical examination the right breast was found to contain a thick hard mass 6 by 8 cm. in the medial upper quadrant with a large mass in the right axilla. Neurological examination revealed ptosis of the left eyelid, marked left-sided facial paresis, and hypesthesia to touch and pinprick over the left anterior part of the tongue and left cornea. Pelvic examination was not recorded.

A needle biopsy of the breast was reported as infiltrating carcinoma with scirrhus reaction. X-ray of the skull showed a slight rarefaction of the superior portion of the left petrous bone close to the inner aspect of the internal auditory canal. Audiometric studies revealed a primary unilateral left-sided hearing loss probably retrocochlear in nature. The clinical diagnosis was carcinoma of the right breast with axillary metastases and neurinoma of the eighth nerve. During the next 3 months the patient was treated in the clinic with

a dose of 8,400 r to the right breast and axilla with some regression of the breast mass. Several months later she was readmitted to the Bronx Municipal Hospital Center because of the sudden onset of left hemiplegia. The clinical impression was cerebral infarction due to occlusion of the right middle cerebral artery, possibly by tumor embolus. Chest x-rays showed metastatic tumor involving the lung and pleura. The patient was given 2,100 mg. of testosterone during the next few months. The clinical course deteriorated progressively and the patient was in coma for the last 6 weeks of life. During this time there were 3 plus proteinuria, increasing generalized edema, and hypoalbuminemia. The final clinical diagnosis was terminal widespread carcinoma of the breast, acoustic neurinoma, and nephrotic syndrome.

At autopsy, the right breast contained a mass which measured 2 by 1.5 by 1 cm. and was hard, irregular, and nonencapsulated, with invasion and fixation of the adjacent fat. Metastatic tumor was found in right axillary, mediastinal, and peribronchial lymph nodes, the fourth lumbar vertebra, the brain, the right lung and both pleural surfaces, and liver.



Fig. 1.—Gross photograph of exocervix showing local nodular elevation without ulceration.

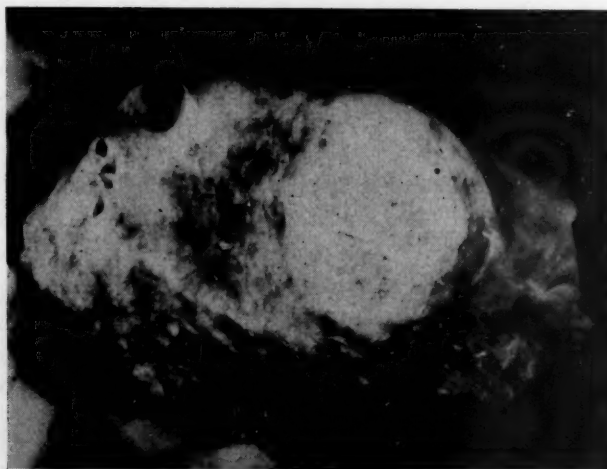


Fig. 2.—Gross photograph of cut surface of cervix taken from site indicated by defect in Fig. 1. Discrete nodule of tumor is present just beneath the surface. There are several adjacent Nabothian cysts.

The kidneys were enlarged (180 grams), pale white, and firm. The cortices were swollen. The cervix measured 3 cm. in diameter. The os was patent and stellate in shape. The exocervix was shiny throughout and gray white with a variegated superimposed blue hue. No gross granularity or ulceration was evident. At 6 o'clock there was an oval nodule measuring 1.4 by 1 cm. which produced some elevation of the overlying external surface to a height of 2 mm. (Fig. 1). On cut section the cervix had a variegated, shiny, tan-brown or gray appearance and beneath the epithelium there were occasional tiny cystic spaces varying from 1 to 2 mm. in size which had a smooth, shiny lining, were unilocular, and contained some clear serous fluid. Between 1 and 2 cm. from the os the cut section showed a well-defined, unencapsulated nodule of opaque, gray-white, dry tissue which was somewhat

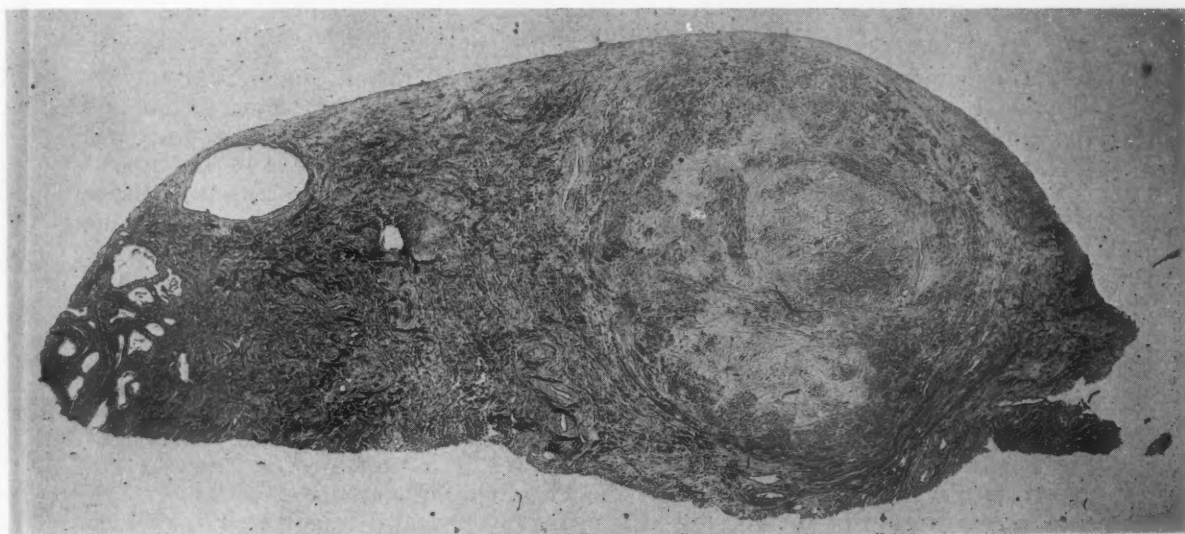


Fig. 3.—Photomicrograph of histologic section of cervix illustrating poorly defined tumor in stroma shown in Fig. 2. (Hematoxylin and eosin.  $\times 7$ .)

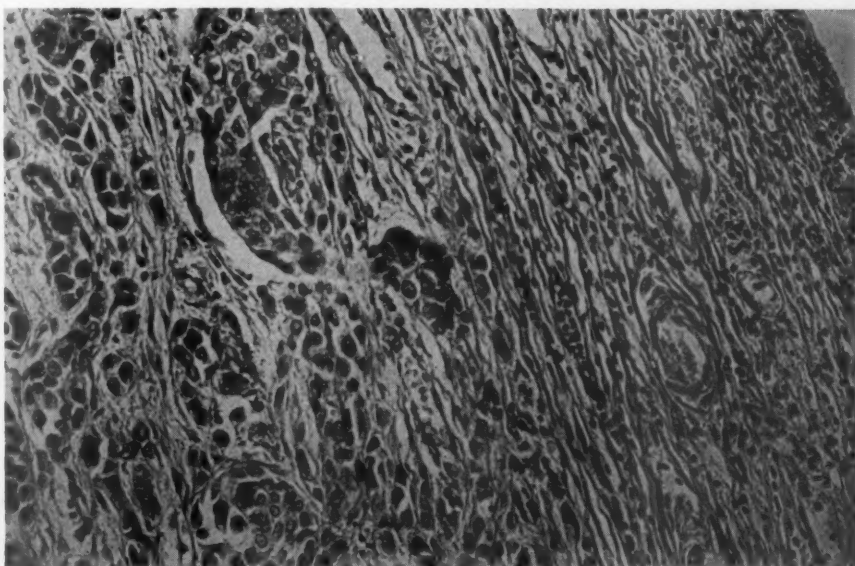


Fig. 4.—Higher magnification of Fig. 3 showing characteristic appearance of metastatic breast carcinoma. (Hematoxylin and eosin.  $\times 250$ ; reduced  $\frac{1}{4}$ .)



firmer than the surrounding stroma. This measured 1.5 by 1.2 by 1 cm. in size (Fig. 2). In addition there was a tumor mass 3 by 2.5 by 1 cm. attached to the eighth cranial nerve in the region of the petrous portion of the temporal bone and pressing upon the left temporal lobe. Microscopically this tumor of the eighth nerve showed the typical pattern of an acoustic neuroma (with masses of wavy flowing cells in a somewhat whorled pattern with some palisading of the nuclei) and contained metastatic carcinoma. Sections of the breast tumor showed a characteristic pattern of primary carcinoma of the breast with cords and clusters of tumor cells in a dense fibrous stroma. A similar pattern was seen in the metastatic sites, including the cervix (Figs. 3 and 4). There was widespread amyloidosis of moderate degree of the adrenals and kidneys and less severe involvement of the arteries of the heart, liver, and spleen.

### Comment

The noteworthy absence of metastatic cancer in the uterine cervix may be explained in several ways. The uterine cervix is a smaller target organ and the actual amount of blood flow is much less compared with other sites such as lung and liver. In addition the general lymphatic drainage of the uterus is away from, rather than toward, the cervix. In general, fibromuscular tissue represents a poor soil for the growth of metastatic tumor. Finally, the uterine cervix is less apt to be carefully examined for the presence of such tumor during routine postmortem studies and such findings are not as easily detected clinically by palpation compared to an enlarged tumor-bearing liver or the appearance of opacities on roentgenograms of the lung.

Although this lesion is rarely reported it may occur more frequently but be overlooked or considered not significant for recording. Some of these metastatic tumors may have been previously mistaken for benign lesions of the cervix such as leiomyomas. In some cases it is possible for these lesions to attain clinical significance, when the histologic appearance of the biopsy of such a cervix may be interpreted as a primary cervical carcinoma<sup>9, 10</sup> for which the patient is subjected to radiation<sup>9</sup> or surgery.

### Summary and Conclusions

A case of metastatic carcinoma of the uterine cervix originating from a primary site in the breast is reported. The literature contains few reports of such an occurrence. Possible reasons for the rarity of such a finding are suggested and relate to such factors as the small size of the target area, the limited blood and lymphatic supply of the uterine cervix, the unfavorable soil for growth of tumor in fibromuscular stroma, and the ease with which this lesion may be overlooked or mistaken for a benign tumor such as leiomyoma.

Failure to consider the possibility of metastatic carcinoma in the cervix may lead to incorrect diagnosis and inappropriate radical therapy.

We wish to express our appreciation to Mr. Milton Kurtz for taking the gross photographs and photomicrographs.

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## ANTIMICROBIAL TREATMENT OF TUBERCULOUS SALPINGITIS\*

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THE purpose of this study is to determine the basic pathology of tuberculous salpingitis and the response of this disease to chemotherapy. The answers to the following questions were sought: Can antimicrobial therapy cure tuberculous salpingitis? Does the tube return to its pretuberculous state so that a normal intrauterine pregnancy may be expected? Is surgery necessary in all cases, and if not, in what type of case is it advisable? How long should antimicrobial therapy be given before and after operation?

### Material and Method

The type of patient suitable for such a study is one in whom a diagnosis of tuberculous salpingitis has been made and who is treated with antimicrobial drugs for a period of time before salpingectomy. We shall present the clinical and pathologic findings in 10 patients treated in this manner. These cases were selected from a much larger group of patients treated for pelvic tuberculosis during the past few years but who are not included in this report for various reasons. Since 10 patients are obviously too small a series from which to draw conclusions, we have included the following aspects of the antimicrobial treatment of tuberculosis: (1) an evaluation of the effect of antimicrobial drugs in cases of extragenital tuberculosis (lung and kidney) where surgical specimens were available for study; (2) analyses of the results of treatment of the cervix, of the endometrium, and of the tubes, as reported in the literature; (3) review of pathologic lesions in the Fallopian tubes of patients who did not receive antimicrobial therapy before operation.

### Evaluation of Antimicrobial Therapy in Other Organs

**Lungs.**—After antituberculosis therapy, the changes reported in resected lesions with healing deal with the clearing of infiltration, resorption of exudate, fibrous contraction of the lesions, and the closure of the cavities with a variety of healing manifestations. There is an accelerated healing of tuberculous foci during chemotherapy. Anatomically this healing is characterized by the more rapid deposition of calcium salts in the necrotic foci and the transformation of granulation tissue into hyalinized connective tissue within the capsule.<sup>1</sup> Amoruso<sup>2</sup> believes that there is a peak of drug therapy effectiveness beyond which there is practically no improvement. This therapeutic critical point varied

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considerably and was reached between the sixth and the eighteenth month of chemotherapy. The lesions resected at this juncture showed tubercle bacilli by microscopic examination in 82 per cent of the operative specimens, and in 27 per cent the bacilli were viable and pathogenic for guinea pigs. Bloch and his co-workers<sup>3</sup> suggest that the optimal period for surgical resection lies within the first 6 months of chemotherapy.

The most effective chemotherapy obviously cannot reconstitute irreversibly destroyed tissue. The problem is to decide whether long-term chemotherapy alone is sufficient or whether certain lesions are inherently hazardous and demand surgical resection in addition to long-term therapy.<sup>4</sup> Despite the availability of several drugs highly effective against tubercle bacilli in vivo, it is becoming increasingly evident from many studies that it is very difficult, if not impossible, to eradicate infection from human patients, even by prolonged chemotherapy. After antimicrobial drugs have ceased to exert their restraining influence on infection, either because the infective organisms have become resistant, or because therapy has been interrupted, only the resistance of the host can prevent reactivation of the disease caused by the surviving bacilli.<sup>5</sup> The past decade has been marked by a better understanding of the potential hazard of residual disease foci and by the demonstration of the practicability of their surgical removal. Pathologic studies of resected specimens have revealed that the nonnecrotic component of tuberculous disease is favorably affected by adequate drug therapy. The variability in the morphologic picture of necrotic lesions, however, indicates that chemotherapy does not have a marked effect on this component.<sup>6</sup>

*Kidney.*—Dick<sup>7</sup> showed that after a 3 month course of streptomycin and PAS considerable fibrosis developed in kidney lesions. Regressive changes developed only in tuberculous lesions active at the onset of treatment. Old, inactive lesions showed little or no change. Following isoniazid therapy for renal tuberculosis, changes became manifest from the second to the eighth week. Relapses were noted occasionally some time after all forms of antimicrobial treatment. Although the cases reported by Dick were treated with short-term therapy, he states that relapses may occur even after prolonged therapy, because of the persistence of organisms in the dormant stage. His bacteriologic and histologic studies suggest that even prolonged chemotherapy will not destroy all the organisms, and this justifies surgery in chronic lesions whenever possible. Lattimer<sup>8</sup> and Greenberger<sup>9</sup> also advise nephrectomy for unilateral renal tuberculosis in selected cases following a course of antituberculosis therapy.

### Treatment of Genital Organs

*Cervix.*—Using the cervix as an index of improvement of genital tuberculosis, Sered, Falls, and Zummo<sup>10</sup> stated that "120 days of streptomycin therapy, preferably given with PAS, will usually result in a marked degree of improvement." From the 7 cases reported they concluded that a minimum of 3 months of streptomycin and PAS was necessary to cause healing of tuberculous cervicitis. It should be noted however, that in all of these cases the tubes and ovaries still showed evidence of tuberculosis at operation. It appears, therefore, that the cervix is not a reliable index to judge the healing of tuberculous tubes.

*Endometrium.*—Several authors<sup>11-15</sup> have reported the results of antimicrobial therapy on tuberculous endometritis. With the therapy employed, there were recurrences in the endometrium in from 20 to 40 per cent of these 387 cases collected from the literature. None of the regimens used is now considered adequate to effect a cure of tuberculosis, however. Halbrecht<sup>12</sup> used

1 Gm. streptomycin 3 times a week in conjunction with PAS daily for 4 months. This is a step in the right direction, but this can still be considered short-term therapy and resulted in recurrences in 35 per cent of his cases. Sutherland<sup>14</sup> and Millar<sup>15</sup> used streptomycin and PAS, or streptomycin and isoniazid for 3 months. Not only is this too short a period, but it is now generally agreed that the intramuscular administration of 1 Gm. streptomycin or dihydrostreptomycin to the average adult with tuberculosis 2 or 3 times a week is as effective therapeutically as daily administration of the same dose. This interrupted regimen produces fewer toxic reactions and fewer drug-resistant strains of tubercle bacilli and permits the drugs to retain their therapeutic effect for an indefinite time.<sup>16</sup>

There is reason to believe that in some instances antimicrobial therapy can bring about histologic and bacteriologic cure of endometrial tuberculosis, but this does not mean there is the same striking effect upon the tubal disease. Segovia and associates<sup>17</sup> showed that 24 of 28 patients whose endometria were cleared of tuberculosis by antimicrobial therapy had tuberculosis of the tubes at the time of operation. Since endometrial disease is usually limited to the mucous membranes which are shed every month, is free of caseation, and is more recent than the tubal involvement, a favorable result is to be expected. Tuberculous endometritis is secondary to tuberculous salpingitis, however, and cure of the former should not be regarded as cure of the latter. There is no accurate method of assessing the condition of the Fallopian tubes short of laparotomy and extensive study of the tubes. An increasing group of workers<sup>18-22</sup> have stressed the importance of bacteriologic examination of menstrual blood in both the initial diagnosis and in determining recurrence of female genital tuberculosis. Menstrual blood has been reported positive for tubercle bacilli when endometrial curettage has been negative on both histologic and bacteriologic examination. This may be further evidence that the endometrial lesion can be cured while the tubal lesion remains active.

**Fallopian Tubes.**—The results of antimicrobial therapy on tuberculous salpingitis in patients subjected to surgery has been compiled from the literature.<sup>12, 17, 23-26</sup> In 90 to 100 per cent of patients treated for 3 months or less, the tubes showed histologic evidence of tuberculosis. Of 4 patients treated by Halbrecht<sup>12</sup> for 5 to 6 months, 3 showed residual tuberculosis. It appears from the 95 cases collected from the literature that therapy for 3 months or less does not cure tuberculous salpingitis. The extent of the lesion in the tube before the beginning of therapy, so important for proper evaluation, was not stated in these reports, however.

The question arises whether the results of the various regimens of chemotherapy, with or without operation, in extragenital tuberculosis can be used as a basis for treatment of female genital tuberculosis. Haines<sup>27</sup> stated that the histologic feature of a tuberculous lesion follows a fairly uniform pattern regardless of the organ or tissue infected. D'Esopo<sup>28</sup> believes, "by and large, the virtues and frailties of the regimens that have been discussed [long-term multiple drug therapy] are as applicable to extrapulmonary as they are to pulmonary tuberculosis."

### Present Study

We shall present the clinical and pathologic results in a group of patients who received multiple drug therapy for varying periods of time, up to 3 years, followed by operative removal of the Fallopian tubes.

**CASE 1.**—A 24-year-old married, nulligravid Negro woman was admitted to The New York Lying-In Hospital in September, 1952, because of a bloody vaginal discharge which



had been recurring since her marriage 6 years before. In 1951 she had an appendectomy at another hospital and was told that she had tuberculous peritonitis and tuberculosis of the appendix. No specific treatment was offered for this condition at that time.

Pelvic examination showed the uterus to be slightly enlarged and there were firm, thick masses in both adnexal regions. The cervix appeared hypertrophied and showed a laceration. A dilatation and curettage and biopsy of the cervix revealed tuberculous endometritis and tuberculosis of the cervix. After 6 weeks of therapy with streptomycin and PAS, a total hysterectomy and bilateral salpingectomy and left oophorectomy were performed.

Histologic examination of the organs removed disclosed tuberculosis of the uterus, cervix, tubes, and ovary. The microscopic appearance of the tube is shown in Fig. 1. Following operation, modified bed rest was prescribed for 3 months and antimicrobial therapy was continued for 9 months. She has been examined at regular intervals and was last seen in November, 1956. Chest x-rays have been repeatedly negative and her general condition is good.

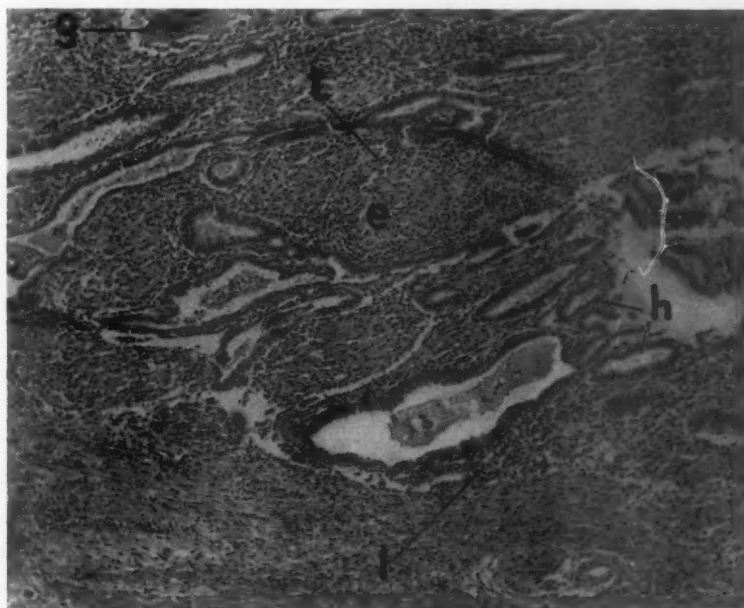


Fig. 1.—Fallopian tube after 6 weeks of antimicrobial treatment. Hyperplastic tuberculous with proliferative changes in the tubal epithelium which shows both hypertrophy and hyperplasia (*h*). The stroma of the villus folds shows a marked epithelioid reaction (*e*) and lymphocytic infiltration (*l*). There is some loss of delineation of isolated tubercle structure (*t*). The giant cells (*g*) have lost their Langhans pattern. (X100; reduced  $\frac{1}{6}$ .)

CASE 2.—A 34-year-old white, single Belgian woman was admitted to The New York Hospital in October, 1954, because of abdominal pain of 10 weeks' duration. In 1939 she had pleurisy with effusion and in 1940 a fusion operation for tuberculosis of the spine, following which she was treated with bed rest for 2 years.

Examination under anesthesia showed the introitus to be virginal. On rectal examination bilateral tuboovarian masses were palpable. A dilatation and curettage done on Oct. 29, 1954, was negative for tuberculosis. After 6 weeks of therapy with isoniazid and streptomycin, a total hysterectomy and bilateral salpingo-oophorectomy were performed. (It was felt that preoperative therapy with the antimicrobial drugs should be continued for a longer period. However, the patient desired to return to Belgium and requested that operation be done at this time.)

At operation all the pelvic viscera were matted together to small and large bowel, omentum, and bladder. Numerous tubercles were noted on the intestines. Tubes and ovaries

were firmly adherent and could not be separated. Histologic examination of the organs removed showed no tuberculosis in the uterus or ovaries, but bilateral tuberculous salpingitis was present as shown in Figs. 2 and 3.

Postoperatively it was advised that the antimicrobial drugs be continued for 2 years in view of the activity of the tuberculosis as noted at operation. This has been done and a report from the patient's physician in December, 1957, stated that she is in good health and has had no further recurrence of tuberculosis.

Fig. 2.

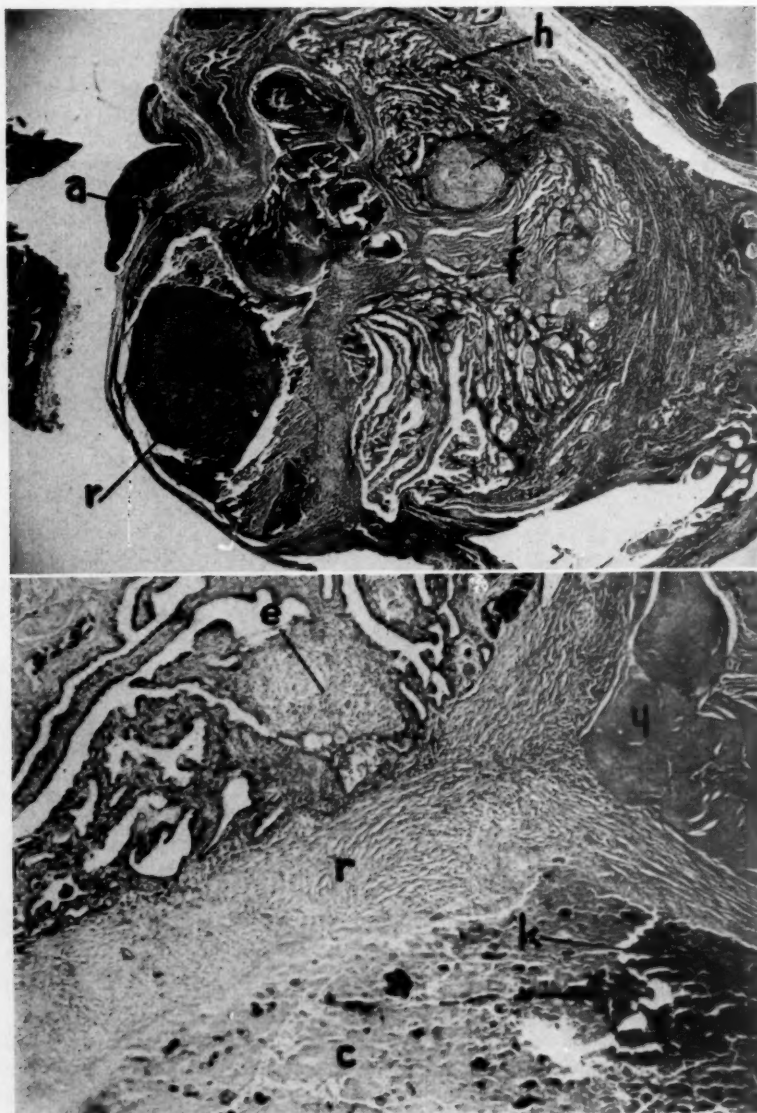


Fig. 3.

Fig. 2.—Fallopian tube after 6 weeks of antimicrobial therapy. Conglomerate tubercle with well-developed reticulum (*r*) and collagen (*a*) formation. There are hypertrophied villi (*h*) between the areas of fibrosis (*f*). Epithelioid tubercles (*e*) are seen in the hyperplastic mucosa (*h*). (X10; reduced  $\frac{1}{6}$ .)

Fig. 3.—Another section of tube from same patient as in Fig. 2. This section shows various stages of tuberculous caseation (*c*), hyalinization (*y*), and calcification (*k*). There is some loosening of the epithelioid tubercle (*e*) and transformation into reticulum (*r*). (X40; reduced  $\frac{1}{6}$ .)

CASE 3.—A 34-year-old white married, nulligravid Puerto Rican woman was admitted to The New York Lying-In Hospital in November, 1952, because of intermenstrual bleeding of 3 months' duration. A biopsy of the cervix and a dilatation and curettage had been performed at another hospital where a diagnosis of tuberculous endometritis was made. The patient was then transferred to The New York Hospital. Pelvic examination revealed the uterus to be of normal size. The cervix was the site of several healed biopsy scars and there was moderate thickening in both adnexal regions. After 8 weeks of chemotherapy a total hysterectomy and bilateral salpingo-oophorectomy were performed. At operation there were thick, dense adhesions binding all the pelvic viscera together. Histologic examination of the removed genital organs showed no evidence of tuberculosis in the uterus and ovaries. Tuberculosis of the tubes is shown in Fig. 4.

Following operation the patient was continued on antimicrobial drugs for 9 months. She has remained well and when last seen 4 years postoperatively in January, 1957, had no complaints except for menopausal symptoms for which treatment was prescribed.

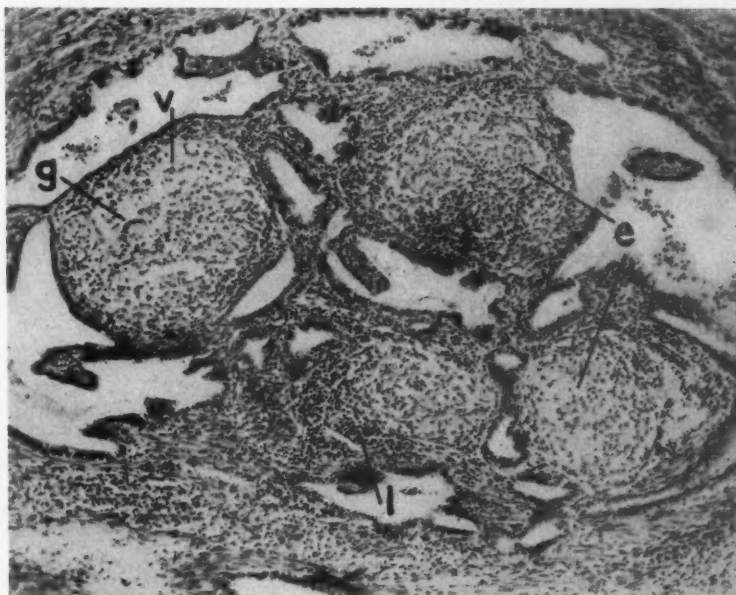


Fig. 4.—Fallopian tube after 8 weeks of antimicrobial therapy. Pseudogland formation due to fusion of the villus folds. "Atrophic" epithelioid tubercles (*e*) showing marked vacuolization (*v*). A few giant cells (*g*) are present and some of these are distorted. The lymphocytic reaction (*l*) is not prominent. There is no caseation. ( $\times 100$ ; reduced  $\frac{1}{2}$ .)

CASE 4.—A 39-year-old Negro woman was admitted to the hospital in December, 1956, because of menometrorrhagia of 6 months' duration. The past history was negative for tuberculosis; a chest x-ray was reported as negative 2 months previously. She had two children, 17 and 11 years of age. In 1947 the right Fallopian tube was removed for an ectopic pregnancy at another hospital. (These slides are not available for review.) On pelvic examination there was an 8 by 10 cm. cystic mass adherent to the uterus in the left adnexal region. The uterus was irregularly enlarged to 3 times normal size. A dilatation and curettage showed tuberculous endometritis.

The patient was given streptomycin and PAS for 3 months, following which a total hysterectomy and left salpingo-oophorectomy were performed. The sections of the tube shown in Fig. 5 reveal the presence of tuberculosis. Following operation she was continued on antimicrobial therapy which she is still receiving. Her general condition is good and she has no complaints.

CASE 5.—A 37-year-old white nulligravid, married woman was admitted to The New York Hospital in May, 1955, because of abdominal pain of 5 months' duration. In 1947 a



laparotomy was performed at another hospital for abdominal pain, at which time she was told she had peritoneal tuberculosis. On pelvic examination the uterus was felt to be of normal size, deviated to the right, and tender on motion. There were tenderness and induration in both adnexal regions. A dilatation and curettage showed tuberculosis of the endometrium. The patient was put at bed rest and started on streptomycin and isoniazid. After one month of treatment in the hospital, the patient was discharged home on modified activity and antimicrobial therapy. She was readmitted to the hospital in October, 1955. Symptomatically she was not improved and continued to have lower abdominal pain. On pelvic examination the induration was still present in the adnexal regions. After 5 months of therapy a total hysterectomy and bilateral salpingo-oophorectomy were performed. Histologic examination of the organs removed revealed no tuberculosis in the uterus, ovaries, or tubes, but a marked chronic follicular salpingitis and perisalpingitis as shown in Fig. 6.

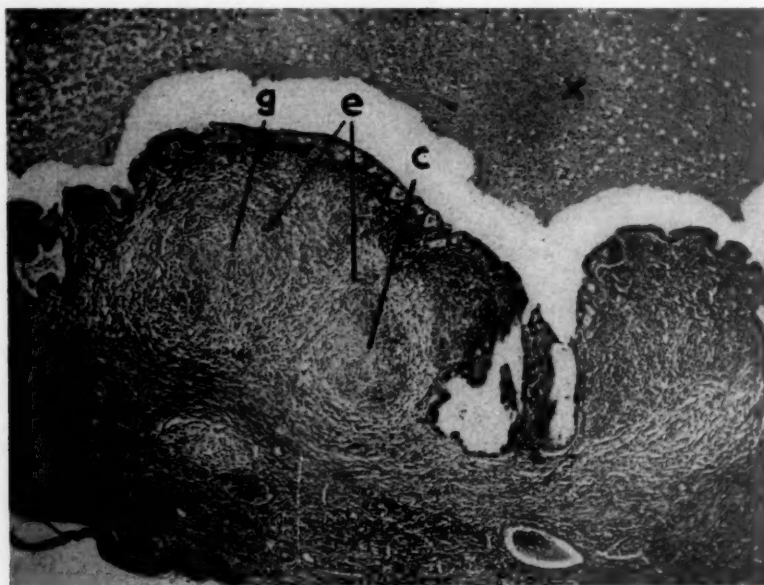


Fig. 5.—Fallopian tube after 3 months of antimicrobial therapy. Exudate is present in the lumen of the tube (*x*). Under the mucosa, in the wall of the tube are several epithelioid tubercles (*e*) containing epithelioid cells and giant cells (*g*). Some tubercles show central caseation (*c*). ( $\times 45$ ; reduced  $\frac{1}{4}$ .)

Postoperatively streptomycin was continued for 9 months and isoniazid was given for 21 months. The patient's general condition is good and she is now free of symptoms except for hot flushes which have responded to the oral administration of estrogenic hormones.

**CASE 6.**—A 24-year-old white single woman was admitted to The New York Lying-In Hospital in August, 1954, because of lower abdominal pain and frequent menstrual periods for the past 6 months. In 1945 she developed pulmonary tuberculosis and in 1946 a right upper lobectomy and right-sided thoracoplasty were performed. Her menstrual periods began at the age of 12, occurred every 30 days, and lasted 5 days, until 1945, when she developed pulmonary tuberculosis. Since that time her periods have occurred every 2 weeks. She had been placed on antimicrobial therapy in 1953 by her phthisiologist (streptomycin, isoniazid, and PAS), and this was continued up to the time of her admission to the hospital.

Pelvic examination revealed a virginal introitus. On rectal examination the uterus appeared slightly enlarged and there were tenderness and induration in both adnexal regions. After 10 months of antimicrobial therapy, a dilatation and curettage, bilateral salpingectomy, partial resection of the right ovary, and appendectomy were performed. At operation the uterus was slightly enlarged, the left tube was nodular with several white plaques on its



proximal third, and the left ovary appeared normal. The right ovary was enlarged to 3 times the normal size and the right tube was irregular and nodular, having the appearance of salpingitis isthmica nodosa.

Histologic examination of the tubes showed chronic follicular salpingitis without evidence of active tuberculosis and a hemorrhagic cyst of the right ovary. Following operation the patient was continued on isoniazid and PAS for 6 months. Her last examination in November, 1957, showed the menses to be normal, occurring every 26 days, and pelvic examination was unremarkable. She has had no further abdominal complaints.

CASE 7.—A 34-year-old Negro nulligravida was admitted to The New York Lying-In Hospital in October, 1953, for menorrhagia of 3 months' duration. In 1940 she contracted pulmonary tuberculosis with pleurisy. On pelvic examination a mass which was thought to be an ovarian cyst was palpable in the right adnexal region. The remainder of the pelvic

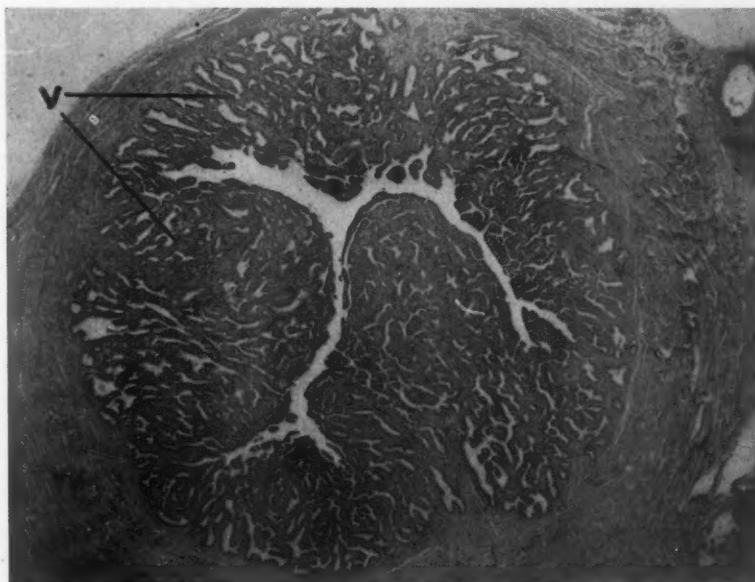


Fig. 6.—Fallopian tube after 5 months of antimicrobial therapy. There is a marked hypertrophy of the villus folds (*v*) with pseudogland formation. Wall of tube at (*w*). The lumen is markedly narrowed. No evidence of tuberculosis is present. ( $\times 25$ ; reduced  $\frac{1}{2}$ .)

examination was normal. A dilatation and curettage revealed tuberculosis of the endometrium. Streptomycin and isoniazid were started, and another curettage performed in May, 1954, showed no evidence of tuberculosis. A hysterosalpingogram in December, 1954, showed bilateral tubal occlusion. Streptomycin and isoniazid were continued for 18 months, and then the patient moved to another state. She returned to The New York Lying-In Hospital in March, 1957, complaining of severe right lower quadrant pain and swelling of the abdomen of one week's duration. She had no menstrual irregularities and had felt well up to the time of her present illness.

Pelvic examination showed a large mass filling the right side of the pelvis. A smaller mass was palpable in the region of the left adnexa. A total hysterectomy and bilateral salpingo-oophorectomy were performed. Pathologic examination of the organs removed showed an endometrial cyst of the right ovary with perioophoritis; the right tube showed chronic follicular salpingitis with areas of salpingitis isthmica nodosa. The left ovary was the site of corpus luteum and hemorrhagic cysts, endometriosis, and perioophoritis. The left tube showed chronic follicular salpingitis. The uterus contained an endometrial polyp.

Postoperatively the patient did well. She was not given antimicrobial therapy, and when last seen 9 months following operation she had no complaints.

CASE 8.—A 25-year-old single Negro woman was first admitted to The New York Hospital in July, 1953, because of amenorrhea of 10 months' duration. Pelvic examination showed the uterus to be small and displaced to the left. The cervix appeared normal. In the right adnexal region was a tender, fluctuant mass, measuring 5 by 5 cm. The left tube was thickened and irregular. Dilatation and curettage revealed tuberculous endometritis. The patient was put at bed rest and started on antimicrobial therapy. After 3 weeks she was discharged from the hospital to continue therapy at home. A second curettage after 6 weeks of antimicrobial therapy showed that tuberculous endometritis was still present. She was readmitted to the hospital after 10 months of therapy for further evaluation. This time she was asymptomatic, except for the continuing amenorrhea and pain in the right lower quadrant. The tender mass on the right side was the same size as on the previous examination 10 months before. A dilatation and curettage and a laparotomy were performed in

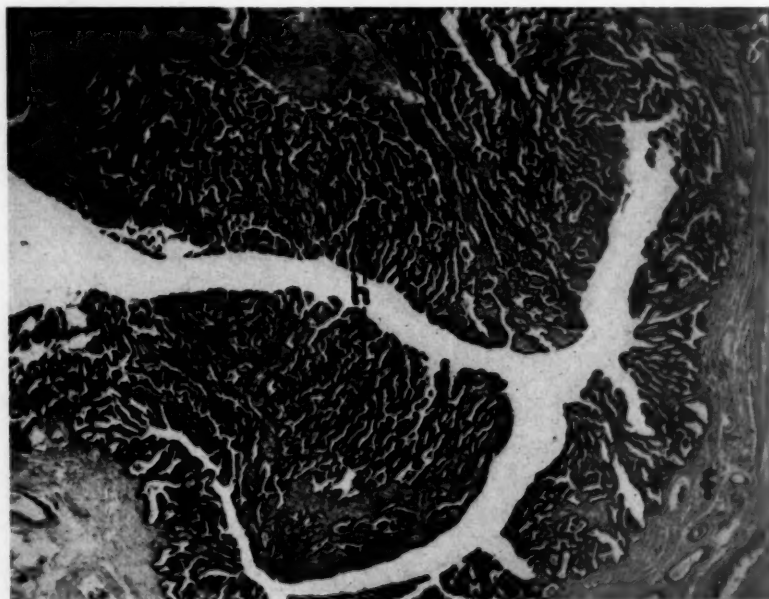


Fig. 7.—Right Fallopian tube after 10 months of treatment with antimicrobials. There is marked hyperplasia of the villi (*h*) with fusion giving the appearance of pseudogland formation. The stroma (*s*) shows fibrous thickening. The wall of the tube shows fibrosis (*f*). No evidence of tuberculosis. ( $\times 20$ ; reduced  $\frac{1}{5}$ .)

June, 1954. The right tube was swollen, red, and stretched over the cystic mass. The left tube was very slightly injected, and the ovary did not appear unusual. A right salpingo-oophorectomy and appendectomy were performed. Histologic examination showed the cystic mass to be a large corpus hemorrhagicum lined with luteal cells. The tube showed a marked chronic follicular salpingitis (Fig. 7). Endometrial curettings were insufficient for diagnosis.

In April, 1955, she was readmitted to the hospital because of progressive pain and tenderness in the left lower quadrant. She had been on antimicrobial therapy for 20 months up to this time. Pelvic examination showed a small nodule in the region of the left adnexa. A total hysterectomy and left salpingo-oophorectomy and removal of a caseous nodule in the left pelvic wall were performed. The uterus appeared normal, the left tube and ovary appeared grossly normal. The nodule in the lateral pelvic wall measured  $1\frac{1}{2}$  cm. and showed caseation on microscopic examination. Histologic examination also showed adenomyosis of the uterus with minimal chronic endocervicitis and endometriosis. The ovary contained several follicular cysts and the tube showed a chronic follicular salpingitis similar to that shown in the opposite tube at the previous operation. Streptomycin and isoniazid were continued postoperatively until August, 1955, when the former was discontinued. Isoniazid was

discontinued in January, 1956. Because of hot flushes, estrogenic hormones were given orally. The patient was last seen in June, 1956, when her only complaints were those referable to the surgical menopause.

CASE 9.—A 28-year-old white married, nulligravid Italian woman was admitted to The New York Hospital in December, 1953, because of infertility of 3½ years' duration. She stated that 10 years previously she had had a laparotomy for peritonitis in Italy following which she received x-ray treatments to the abdomen. Chest x-ray on admission showed

Fig. 8.

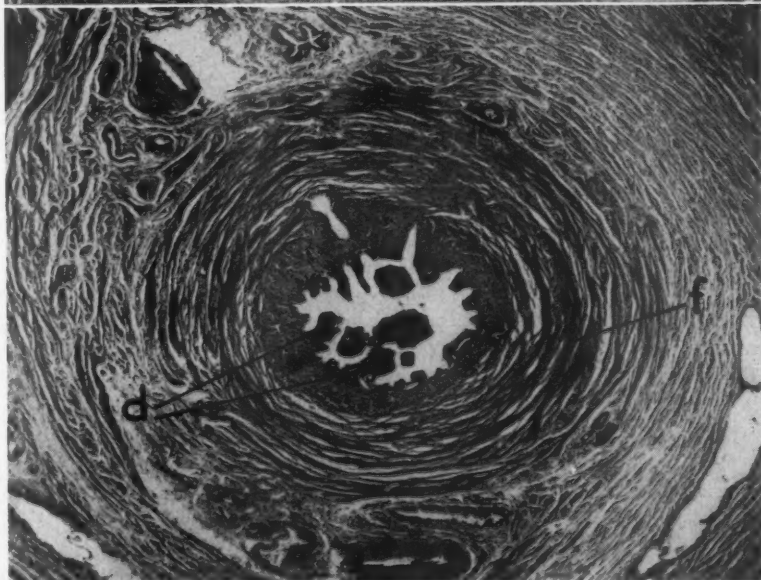


Fig. 9.

Fig. 8.—Fallopian tube before treatment. There are several tubercles (*t*) with caseation (*o*) and giant cells (*g*) in an area of salpingitis isthmica nodosa (*i*). ( $\times 33$ ; reduced  $\frac{1}{2}$ .)

Fig. 9.—Fallopian tube after antimicrobial treatment for 2 years. Same patient as in Fig. 8. There is clubbing and retraction of the villus folds (*d*). Marked fibrosis (*f*) is seen under the epithelial lining. No evidence of tuberculosis. ( $\times 33$ ; reduced  $\frac{1}{2}$ .)



an old, apparently healed lesion in the left lung. On pelvic examination the uterus was anterior, normal in size, and the cervix appeared normal. There was induration in both adnexal regions, greater on the left side.

A dilatation and curettage showed advanced secretory endometrium. The patient was discharged and followed in the infertility clinic where persistent filling defects in the uterine cavity and bilateral tubal occlusion were demonstrated by repeated hystero-grams. She was readmitted to the hospital in January, 1955, when pelvic examination showed the uterus to be deviated slightly to the right, but otherwise normal. In the left adnexal region there was a cystic mass measuring 5 cm. in diameter and on the right side the tube appeared enlarged and indurated. A dilatation and curettage and a bilateral tubal plastic operation were performed with the resection of portions of both tubes and a left ovarian cyst. The uterus appeared normal. There were several small caseous areas measuring 0.5 to 1 cm. on both tubes. Histologic examination of the tissue removed showed bilateral tuberculous salpingitis and a serous cyst of the ovary. Section of the tube is shown in Fig. 8.

Following operation the patient was kept on complete bed rest and started on streptomycin and isoniazid. She was discharged from the hospital after 3 weeks of bed rest and followed in the clinic. One year after operation she developed lower abdominal pain associated with dysmenorrhea and dyspareunia. These symptoms became progressively worse although antimicrobial therapy was being continued. In January, 1957, after 2 years of antituberculosis therapy, a dilatation and curettage and a laparotomy were performed. After separation of the adhesions the uterus appeared normal. The remainder of both tubes and a cystic right ovary were removed and a presacral neurectomy performed. The right ovary showed a follicular granulosa-cell cyst and marked perioophoritis. The right tube showed chronic follicular salpingitis (Fig. 9); the left tube showed chronic follicular salpingitis in an area of salpingitis isthmica nodosa; the uterine curettings did not show tuberculosis.

She has been relieved of her symptoms and has gained weight, and her present condition is good. Antimicrobial therapy was discontinued 12 months after operation.

**CASE 10.**—A 23-year-old white married, nulligravid Ecuadorian woman was first admitted to The New York Lying-In Hospital in June, 1953, because of lower abdominal pain of one year's duration and a history of infertility for one year. Pelvic examination showed the uterus to be anterior and of normal size; the right adnexa appeared normal. In the left adnexa was a small tuboovarian mass which was not thought to be significant. A dilatation and curettage revealed tuberculous endometritis. The patient was placed at bed rest and given PAS, streptomycin, and isoniazid. After 4 weeks she was discharged from the hospital to continue the antimicrobial therapy at home.

In August, 1953, a dilatation and curettage showed no evidence of tuberculosis. In November, 1954, she was readmitted to the hospital where another curettage and biopsy of the cervix were done. Bacteriologic examination of the biopsy specimen of the cervix revealed tubercle bacilli on culture and on guinea pig inoculation. There was no evidence of tuberculosis on histologic examination. She was readmitted to the hospital in April, 1955, because of continued left lower quadrant pain. Laparotomy at this time revealed numerous adhesions in the pelvis. The left tube and ovary were bound down in the cul-de-sac and adherent to the bowel. On the right side the tube appeared to be somewhat nodular and thickened. Several small nodules were removed from the ovary. The left tube was pale, thickened, and nodular. Because of the patient's desire to become pregnant, only biopsies of the nodules in the pelvis were taken and the appendix was removed. Up to the time of this operation she had received antimicrobial drugs for 22 months. Histologic examination of the tissue removed from the right ovary revealed a calcified hyalinized nodule.

In August, 1956, the patient was readmitted to the hospital because of increasing lower abdominal pain which was worse at the time of her period. She also complained of dysmenorrhea and dyspareunia. A dilatation and curettage again revealed no evidence of tuberculosis. This patient had now received antimicrobial therapy for over 3 years. She still complained of lower abdominal pain for which no cause outside the genital tract could be discovered. After long and repeated discussion with the patient and her husband, another



operation was decided upon at which the removal of both tubes was contemplated. Accordingly on Aug. 5, 1956, a left salpingectomy, right salpingo-oophorectomy, and presacral neurectomy were performed. Histologic examination of the removed organs showed extensive chronic follicular salpingitis (Fig. 10). Isoniazid was continued postoperatively for 6 months. In February, 1958, the patient had no complaints referable to the pelvis, had gained weight, and was feeling well.

### Type of Disease

A clinical classification of female genital tuberculosis into advanced and minimal as an aid to outlining therapy has previously been suggested.<sup>29</sup>

*Untreated Tubal Tuberculosis.*—The histologic changes in the tuberculous tubes removed from patients who did not receive antimicrobial therapy are described so that these lesions can be compared with those in treated patients.

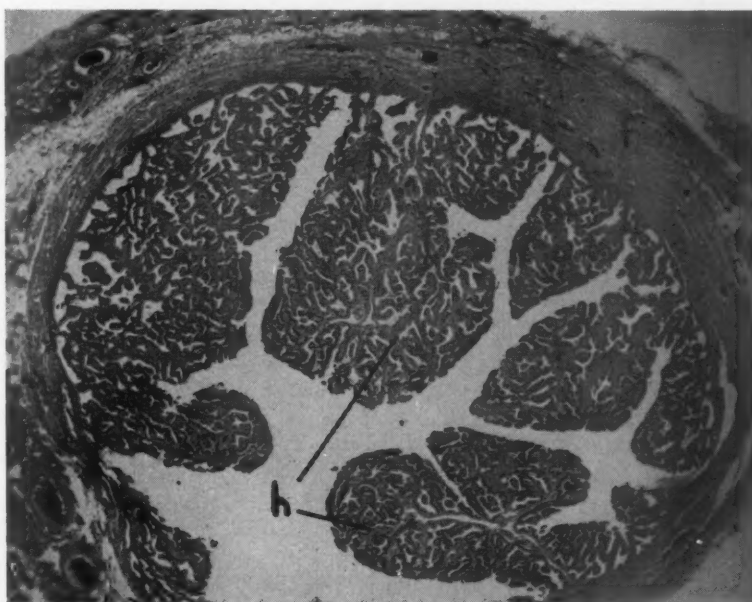


Fig. 10.—Fallopian tube after 3 years of treatment with antimicrobial drugs. There is fusion of the villi and hypertrophy of the folds (h) with pseudogland formation. The wall of the tube shows some fibrosis (f). No evidence of tuberculosis. (×20; reduced 1/4.)

Figs. 11-15 show various stages of progression and regression in untreated tuberculous salpingitis, from replacement of the entire tube by a caseating abscess to apparently spontaneously healed areas showing fibrosis and calcification. In some tubes the villi are completely destroyed and the tubal wall thickened, while in others the tubal lumen is distended with inflammatory exudate. Some sections show marked epithelial hyperplasia with numerous tubercles, epithelioid and giant cells, granulation tissue, and lymphocytic infiltration.

*Tubal Tuberculosis After Short-Term Chemotherapy.*—The following pathologic changes were noted in the various sections of Fallopian tubes in patients treated with antimicrobial drugs for periods up to 3 months. There was a loss of the sharp delineation of the tubercles with vacuolization of the epithelioid cells. Some giant cells appeared “naked,” that is, they were not surrounded by epithelioid cells or lymphocytes, whereas other giant cells showed various stages of distortion. Caseation and granulation tissue were

Fig. 11.

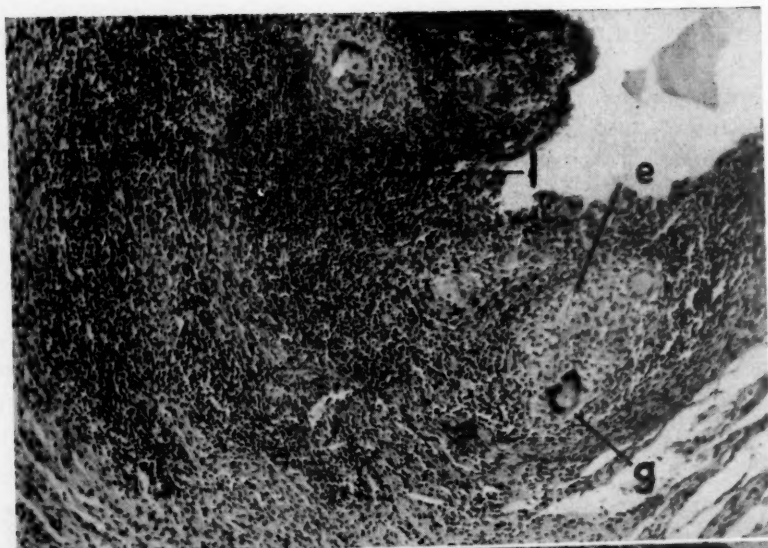


Fig. 12.

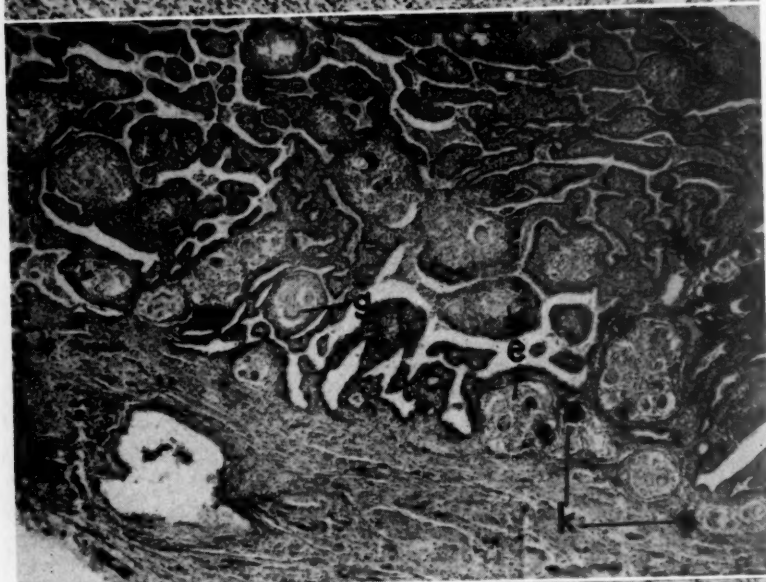
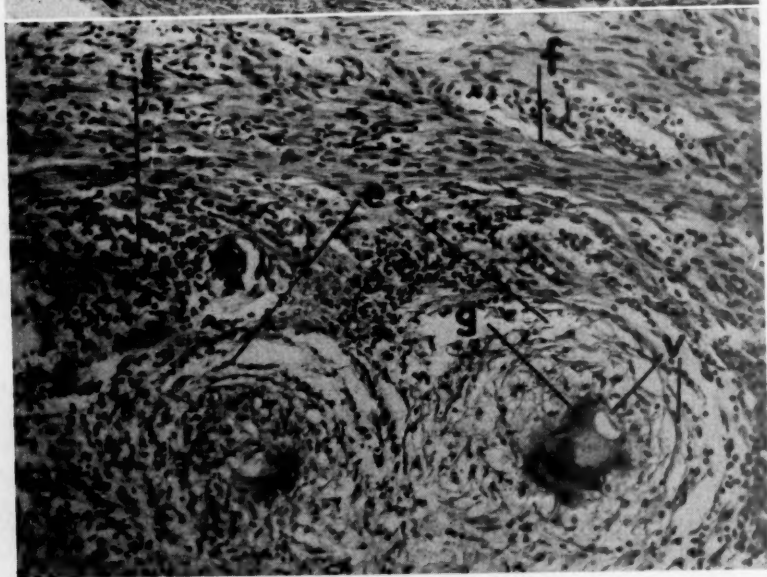


Fig. 13.



Figs. 11-13.—For legends see opposite page.

Fig. 14.



Fig. 15.

Fig. 14.—Caseation at (c). Hyaline fibrosis at (f). Lymphocytic infiltration at (l). (X80; reduced  $\frac{1}{6}$ .)

Fig. 15.—Fusion of villous folds (b). Calcification at (k). Small area of caseation (c). There is very little epithelioid reaction. (Left tube removed in 1939.) (X30; reduced  $\frac{1}{6}$ .)

Fig. 11.—Epithelioid tubercles (e) with giant cells (g). The epithelioid cells show hypertrophy of the nuclei. There is a marked lymphocytic infiltration at (l). (X100; reduced  $\frac{1}{6}$ .)

Fig. 12.—Epithelioid tubercles (e) with giant cells (g) and marked proliferation of the epithellum. Calcific concretions at (k). (X40; reduced  $\frac{1}{6}$ .)

Fig. 13.—Epithelioid tubercles (e) with giant cells (g). There is some vacuolization (v) of the epithelioid cells and of the giant cells. Fibrous tissue reactions at (f). Lymphocytic infiltration at (l). (X160; reduced  $\frac{1}{6}$ .)



present and in some areas fibrosis could be found. Lymphocytes were few in number at the margin of the tubercles. The epithelioid zone was transformed by reticulum and collagen, and fibrosis of the exudate was noted in some instances.

These variations in the microscopic appearance of tuberculous salpingitis occurred in different patients and in different sections of the same tube. It is not possible, however, to determine from these sections whether the healing process began before the inception of drug therapy.

**Fallopian Tubes After Long-Term Chemotherapy.**—Following long-term chemotherapy the process of healing continues and may reach a stage where tuberculosis can no longer be recognized. In our cases fibrous thickening of the stroma occurred with fibrosis under the epithelial layer and increased collagen formation. In some instances clubbing and retraction of the villi were noted, and in others, a marked hypertrophy of the villus folds with fusion and pseudogland formation. The final stages of healing no doubt differ for the minimal, compared to the advanced lesions, depending on the amount of destruction of the tubal parenchyma at the start of treatment. If the mucosa of the tube has been destroyed by caseation, one can hardly expect a return to the normal architecture of the tube.

Although Auerbach<sup>30</sup> is of the opinion that after long-term chemotherapy the pathologic changes in tuberculous lesions can be differentiated from those in which healing has occurred without benefit of drugs, others believe that while drugs increase the rate of healing the final individual pathologic lesions are no different from the untreated ones. To a great extent the differences in healing depend on the time interval between the onset of the tuberculous infection and the initiation of chemotherapy as well as on the duration of therapy.

### Comment

#### *Can antimicrobial therapy cure tuberculous salpingitis?*

Short-term antimicrobial therapy (3 months or less) does not cure tuberculous salpingitis. This is apparent from the 95 cases collected from the literature in which the tubes showed histologic evidence of tuberculosis in 90 to 100 per cent of the cases, as well as from the patients treated in our series for 3 months or less. Long-term therapy has not been used in sufficient number of advanced cases to determine whether it will effect a cure. Our policy has been to remove enlarged tuberculous tubes together with the uterus and ovaries when indicated after 3 to 4 months of antimicrobial therapy. We have explained our rationale for this procedure in previous papers.<sup>29, 31</sup> This is in accord with the present concepts of treatment of advanced tuberculosis in other parts of the body.

In our cases of minimal tuberculous salpingitis, long-term therapy (10 months to 3 years) has apparently resulted in healing of the tuberculous lesions. It is not always easy to differentiate clinically between advanced and minimal tuberculous salpingitis, however. Our policy at present is to treat minimal disease for 2 years or longer and to follow these patients indefinitely. We have not hesitated to operate upon such patients if signs and symptoms of recurrent disease appear.

#### *Does the tube return to its pretuberculous state so that a normal pregnancy may be expected?*

In our experience the answer is no. We are aware that a few pregnancies have been reported following a diagnosis of tuberculous endometritis, but most



of these have terminated in abortion, ectopic pregnancy, or premature delivery.<sup>32-35</sup> In some reports of pregnancy following tuberculous endometritis the case histories and photographs presented do not convince us that tuberculosis was present. The practically complete destruction of the mucosa in the advanced cases and the marked follicular salpingitis with hypertrophy of the villi in the minimal cases, in the patients we have studied, leave little hope for the occurrence of a normal intrauterine pregnancy. In the rare instances where pregnancy does occur following antimicrobial treatment of genital tuberculosis, there is a 4 to 1 chance that a tubal pregnancy or an abortion will occur.<sup>32</sup>

*Is operation necessary in all cases, and if not, in what type of case is it advisable?*

We believe operation is indicated in all patients with advanced pelvic tuberculosis following a course of antimicrobial therapy. In patients with minimum disease we advise antimicrobial therapy for 2 years or longer. We have not followed a sufficient number of patients long enough on this latter regimen to determine whether recurrences will appear. These patients should be kept under constant surveillance after therapy is discontinued.

*How long should antimicrobial therapy be given before and after operation?*

We recommend that combined therapy—either streptomycin, PAS, and isoniazid, or streptomycin and isoniazid—be given for 3 to 4 months before operation is attempted. The dosage we use is 1 Gm. streptomycin, intramuscularly, daily, for 2 weeks and then 1 Gm. twice a week; 12 Gm. PAS daily, orally, in 3 or 4 divided doses; 300 mg. isoniazid daily in 3 divided doses. There appears to be no valid reason to perform operation in a woman known to have genital tuberculosis without a preoperative course of anti-tuberculosis drugs.

Postoperatively antimicrobial therapy should be given for approximately one year. Combined therapy should be continued in the same dosage as before operation. If there is a possibility that some tuberculous tissue has not been removed at operation, we advise continuing therapy for 18 to 24 months.

Drug therapy is most effective against recent tuberculosis, that is, against disease that has been present for less than 6 months. From several studies on the natural history of tuberculous salpingitis, it has been repeatedly shown that tuberculosis has been present in the tubes from one to 20 years before it is diagnosed.<sup>13, 36, 37</sup> Burns<sup>38</sup> stated that the average duration between onset and diagnosis of genital tuberculosis is 8 years. Pelvic invasion with tubercle bacilli apparently often occurs within 6 weeks to 6 months of the primary infection in the lung. When primary tuberculosis infection occurs in early childhood, there is little risk of subsequent dissemination to the genital tract. When the tuberculous bacilleemia following primary infection coincides with early adolescence or early maturity, there seems to be a special vulnerability of the genital tract, and the tubes in particular, to tuberculous infection.

### Summary

Patients with tuberculous salpingitis treated for 3 months or less with antimicrobial drugs show histologic evidence of tuberculosis in the tubes in approximately 90 per cent of the cases.

Following long-term therapy (10 months to 3 years) in patients with minimal pelvic tuberculosis, no evidence of active tuberculosis was apparent on histologic section of the Fallopian tubes, although residual evidence of

tubal disease was seen. In patients with untreated tuberculous salpingitis, various stages of activity and healing were present and resembled to some extent the lesions in patients treated with short-term chemotherapy.

Recurrences of tuberculosis of the endometrium were reported in 20 to 40 per cent of 387 cases collected from the literature which had been treated from 6 weeks to 3 months with antituberculosis drugs. While such a regimen is not considered adequate, there is reason to believe that in some instances antimicrobial therapy can bring about histologic and bacteriologic cure of endometrial tuberculosis. This does not imply that the lesions in the tubes are also healed for tuberculosis was still present in the Fallopian tubes of the patients who were subjected to operation.

The present trend in the treatment of pulmonary tuberculosis is toward long-term therapy with antimicrobial agents for periods of 18 to 24 months or longer. Even with long-term chemotherapy, however, it is not always possible to eradicate foci of infection, and these have been treated by excision.

I wish to express my deep appreciation to Dr. R. Gordon Douglas, Professor of Obstetrics and Gynecology, Cornell University Medical College and Obstetrician and Gynecologist-In-Chief at The New York Lying-In Hospital for many valuable suggestions, and to Dr. Alfred A. Angrist, Professor and Chairman of the Department of Pathology, Albert Einstein Medical College, for his kindness, patience, and advice in reviewing the numerous histologic sections.

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### Discussion

DR. ALFRED A. ANGRIST.—There are some very practical applications of Dr. Schaefer's work, which I have followed over these years, and it shows how productive a dogged persistent study of any single subject can be. It would seem that when a gynecologist feels some large tubes that are boggy and therefore caseous (and sometimes one can feel the caseous nature of a tube), then that case should be immediately considered for operation. Then the problem is to prepare the patient for the safest type of operation, not with the outlook of curing the tube or of getting that caseous tube and the ovarian abscess to resolve to normal, but to reduce the infectivity of the tuberculosis so that the operation is safer and any complications reduced to a minimum.

The question of endometrial tuberculosis in these cases has been neglected over the years. I was taught, I remember distinctly, that tuberculosis of the endometrium is a distinctly rare entity because it always sloughed off with menses and never had a chance to grow. Actually we know this is not so because endometrial tuberculosis is a common complication of tubal tuberculosis and just in that sequence. I think it is reasonably certain that tuberculosis does not arise from below but comes from a tubal primary hematogenous extension in the vast majority of cases, and then extends to the endometrium.

One aspect of this, though, is still neglected by gynecologists, and that is a rather simple application of the evidence of old healed tuberculosis, because most salpingeal tuberculosis occurs in patients who have a healed lesion, not a presently active lesion.

It is a simple procedure to take some of the menstrual blood and culture it. We have methods today of very specific and accurate cultural detection of tubercle bacilli. This will also serve a good purpose if you want to avoid a curettage at least for a spell.

These are the pragmatic aspects of this work that I can call to your attention. There are other aspects of it that are implied too which I think are often lost sight of. It is not the demonstration of acid-fast bacilli in the specimen that counts because many of those acid-fast bacilli are dead. Particularly in the modern era of specific therapy, many of them will not grow on culture, or if they do grow on culture they will now grow in the form that we know is nonpathogenic for the most susceptible animals. We doubt whether such bacilli are ravaging invaders of the disease tuberculosis. That aspect of the application would be of importance to judge the outcome and the prognosis in these cases when the specimen is removed. When you do come to do operation, that knowledge of the bacteriology will give you a good inkling as to what the ultimate story will be, although we are well aware of the pragmatic fact that the average patient with salpingeal tuberculosis does well following operation.

There are several theoretical matters which I want to note for your attention. You as clinicians can keep in mind in your discussion and in your study of these cases in the future the very common localization of tuberculosis in the tube rather than in the uterine body or in the cervix. The higher incidence obvious in the tube in tuberculosis should raise a question as to whether you are dealing with a tissue specificity of localization and/or a specificity of choice of growth. On that same score it should be noted that tuberculosis of the ovary is a very rare lesion as a disease entity in contrast to tubal tuberculosis. This is true in even far-advanced tuberculosis with extensive miliary dissemination. It is amazing how little



tuberculosis you will see in the ovary in contrast to other tissues in such cases of widespread dissemination. Just as we know that in pulmonary tuberculosis there is a selective localization at the apex, for which nobody has yet given us an adequate explanation, the same problem confronts you as to why the tube is the selective site of localization in the pelvis.

Then there are other enigmas such as why some of the tubes wind up with that beautiful intense hyperplasia of the epithelium and nothing more, as a permanent index of a past tuberculosis. If you show me, in the surgical specimen, that type of hyperplastic mucosal folding with adhesions, or a real follicular salpingitis, I can reassure the resident that if he will cut forty instead of the usual three and four sections, he will run into some good evidence of past tuberculosis. It is that safe a bet. Why does tuberculosis provoke this type of intense hyperplasia? We have not the slightest idea why some tuberculosis of the tube goes on to immediate exudation and is soon transformed to a caseous mass, as occurs in some of the allergic types of tuberculosis in the lung on the one hand, or why in other instances you get a hyperplasia-like mass with epithelioid tubercle reaction. This is mindful of the type of tuberculosis you also often get in tuberculous tenosynovitis. This form of tuberculosis may be so hyperplastic and so diffusely cellular and hypertrophic in its epithelioid reaction without any caseation and without even giant cells as to be mistaken not infrequently for sarcoma. Why that peculiar tissue reaction occurs sometimes in a tube, and exclusively so, is another mystery, in contrast to a tube in another case that will show the characteristic focal caseation, with epithelioid cells and giant cells of the Langhans type that Dr. Schaefer showed so beautifully.

There are other mysteries, such as the process of healing in these tubes. The process of healing in the tube with our newer therapy is exactly the same as it always has been. There is no remarkable transformation in the process or change in it. It is only a more rapid healing process.

Then there is the question of relative infrequency of dissemination from the tube in the female. You know tuberculosis in the male genitals is a much more serious entity than it is in the female. The prostate or the seminal vesicle or epididymis are common sites of localization in the male; and when disseminated miliary tuberculosis secondary to such disease in the male occurs, meningitis is not uncommon. That is a bit unusual in the female in contrast; at least it occurs in a lower percentage.

Then there is the question of whether the healing or progression is linked to the hormone effects. We know that some hormones do control the inflammatory reaction that occurs. Just for the sake of comparison, we know what cortisone does to inflammation. The question is how the estrogenic hormones and progesterone affect the inflammatory response and the tendency to healing, reticulum formation, and fibrosis. There is some effect, of that there is no doubt. Those factors deserve careful study and elucidation and I think you as clinicians may help us understand these effects on the pathological processes as they evolve.

DR. GORDON W. DOUGLAS.—The study of 10 cases in this manner is not an easy undertaking. In this country there is no large pool of female tubercular patients readily accessible for study, such as one finds among males under the care of the Veterans Administration. In cooperation with the Chest Service at Bellevue Hospital, we have been able to accumulate 21 cases suitable for treatment according to a standard plan since 1954. After suitable investigation, each patient is placed on drug therapy for at least one year, with pelvic surgery carried out at different times during this year. Among 16 patients in whom studies are complete, we have found no evidence of endometrial tuberculosis persisting after 6 months of treatment. However, patients with clinical evidence of salpingitis, i.e., palpable adnexal masses, have invariably shown active disease after as long as a year of treatment. It seems likely that the use of drugs, while not eliminating the need for surgery, will allow a diversification of treatment.

DR. SCHAEFER (Closing).—I want to thank Dr. Angrist for his discussion. I neglected to mention the use of menstrual blood in both diagnosis and prognosis of pelvic tuberculosis. We have not used bacteriologic examination of menstrual blood in this country as much as



it has been used in Europe. The finding of a positive menstrual culture in cases of healed endometrial tuberculosis we believe is further evidence that the tube is still involved after antimicrobial therapy.

We are at present conducting a study on bacteriologic examination of menstrual blood and when we have a sufficient number of cases we shall report them. We are getting these cases, by the way, from our Sterility Clinic. Reports from European literature show that up to 10 per cent of all the patients in sterility clinics have unrecognized tuberculosis.

Dr. Angrist mentioned that a good many of these resected lesions show tubercle bacilli which are not viable. That is undoubtedly true. In the culture methods recently reported by Hobby and DuBois, however, in which the cultures are continued for long periods of time, viable tubercle bacilli have been demonstrated in the resected necrotic lesions.

Tuberculous oophoritis is a rare condition. Tuberculous perioophoritis, however, in which extension occurs from the tube to the surface of the ovary, is seen in 25 per cent of the cases of tuberculous salpingitis.

Estrogen as therapy of pelvic tuberculosis was mentioned. Max Lurie in Philadelphia used estrogen in rabbits which he inoculated with tuberculosis and found that large doses diminished the spread of tuberculosis in these animals, whereas choriogonadotrophic hormone had the opposite effect. The dosages used were not physiologic for humans, however.

I was happy to hear of Dr. Douglas's cases. We have frequently been told by clinicians that they never have seen a case of pelvic tuberculosis. We think that if the disease is looked for more carefully more cases will be found. The examination of one section of a tube removed at operation may not show tuberculosis. We have done six or seven or more sections of a tube before finding positive evidence of tuberculosis in one area.

In conjunction with the apparent scarcity of cases in this country, we have several times suggested that some society, perhaps our own, or the American College of Obstetricians and Gynecologists, set up a registry where all cases of pelvic tuberculosis, including slides and case histories, would be reported. In a comparatively short period of time a large number of cases could be collected and different forms of treatment assessed.

In the past 6 or 7 years we have treated or seen—and I should not say treated because some of the patients were not treated by us, being private cases of other members of the staff—approximately 75 cases of pelvic tuberculosis. Not all of them fitted into this category we have reported. In some the tubes were not available for study. In some antimicrobial drugs were not used until after operation and in some the diagnosis was not made before operation.



## Obstetrics

### STUDIES OF AMNIOTIC FLUID AND INTERVILLOUS SPACE PRESSURES IN THE RHESUS MONKEY\*

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**S**TUDIES of the vascular pattern of the endometrium and placenta in monkey and man<sup>11, 12, 13</sup> have indicated that placental circulation is regulated less by morphological arrangements than by pressure differentials between the uterine arterioles, the intervillous space (IVS) and the uterine veins. Furthermore, it has been postulated that the myometrial contractions occurring throughout pregnancy augment placental circulation.

The physiological concept of placental circulation has been formulated as follows<sup>12</sup>: "Arterial blood enters the placenta from the endometrial arteries under a head of maternal pressure sufficiently higher than that prevailing in the vast, amorphous lake of the intervillous space so that the incoming stream is driven high up toward the chorionic plate. Gradually this force is spent and lateral dispersion occurs, aided by the villi which, acting as baffles, promote mixing and slowing and, by their own pulsation, effect a mild stirring. Eventually the blood in the intervillous space falls back upon the orifices in the basal plate which connect with maternal veins, and, since there is an additional fall in blood pressure between the intervillous space and the endometrial veins, drainage is accomplished. The pressure differential is further enhanced by the intermittent myometrial contractions (Braxton Hicks) which compress the thin-walled veins, temporarily preventing escape of blood from the placenta and raising the intervillous pressure. When the myometrium relaxes, the elevated intervillous pressure produces rapid drainage."

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Support for this concept of placental circulation was first provided by the work of Woodbury and associates<sup>16, 17</sup> and has come more recently from the laboratory and clinic of R. Caldeyro-Barcia<sup>1, 4</sup> in South America. Payling Wright and associates<sup>18</sup> in England, studying conditions during labor in particular, supply further confirmatory data. Varying figures for the "effective placental pressure" are presented, depending in part upon the technique of determination (differential manometers; tokodynamometer and microballoons; indirect clearance tests, respectively) and upon the point of departure for study. In general the maternal arterial pressure is regarded as 60 to 70 mm. Hg higher than the pressure in the IVS and the latter as appreciably above the 8 mm. Hg of pelvic venous pressure. Myometrial contractions, normally averaging up to 80 mm. Hg, raise the intrauterine and systemic pressures concomitantly. Woodbury<sup>17</sup> has stressed the initial effect of myometrial contractions in forcing blood from the uterine mural vessels into the general circulation and in subsequently constricting uterine vessels to "create resistance to venous outflow from the placenta." Hendricks<sup>7</sup> reaches a similar conclusion in a recent report of hemodynamic studies showing "redistribution" of blood from the maternal venous reservoir during uterine contraction.

Recognition of the need for further documentation of these pressure relationships and for conducting experiments under stringently controlled conditions, led to initiation of a program of study employing the Carnegie colony of rhesus monkeys. The use of this experimental animal has made possible repeated observations in the course of a single pregnancy (up to four, with further observations in the same subject in subsequent pregnancies), observations at earlier stages than would be advisable in humans, and protraction of observations for as many hours at a time as desired.

In the present paper attention is focused upon two specific considerations: the actual values of the pressures in the amniotic cavity and the IVS and their relationship, and pressure differences at various stages of pregnancy. Basic to the latter consideration is the description of circulatory embarrassment at two epochs. The first occurs immediately before "conversion," the crucial period, about halfway through pregnancy, when enlargement of the uterus ceases to occur upon the basis of growth and commences to be effected by stretching alone.<sup>14</sup> The second occurs just before the onset of labor.<sup>15, 18</sup> Observations of intrauterine pressure have therefore been grouped according to three periods: (a) preconversion, (b) mid-pregnancy, and (c) end of pregnancy. Preconversion can be readily diagnosed since the uterus has a characteristic spheroid shape at this time. At conversion, however, the form becomes and remains cylindrical. The earlier limit of the end-of-pregnancy period must therefore be determined in some other way. We have elected to set this limit at 140 days since Hartman<sup>5</sup> showed spontaneous delivery in the rhesus to occur within the range of 146 to 180 days (mean 164 days).

#### Materials and Methods

Healthy, mature monkeys of the Carnegie colony were bred between days 10 and 12 of the cycle as determined by daily vaginal lavage. At the desired

stage the pregnant animal was anesthetized with intravenous pentobarbital sodium. The uterus was exposed by a lower midline incision and the location of the fetus and placentas was determined by palpation and inspection. In cases in which the IVS was to be entered, the exact location of the placentas was ascertained by transillumination of the uterus. A No. 17 gauge, 3 inch needle with stylet was plunged quickly into the amniotic cavity, successful placement being demonstrated by the outflow of amniotic fluid upon withdrawal of the stylet. A polyethylene catheter was then inserted through the needle. In order to keep the lumen of the catheter open a pump delivering 1 c.c. of saline per hour was attached. The pressure required to keep fluid flowing into the amniotic cavity (which is equal to the pressure within the cavity) was recorded by means of a strain gauge connected to a Sanborn four-channel direct-writing recorder. The recorder was calibrated to record in millimeters of mercury.

When it was desired to record the IVS pressure a No. 17 gauge, 3 inch needle with stylet was inserted slowly into one of the placentas. The position of the needle could usually be checked by palpation or direct vision and its location in the IVS was always confirmed on withdrawal of the stylet by the flow of blood characteristic of the IVS. The polyethylene catheter inserted through this needle was also connected to a pump in order to prevent obstruction of the lumen by blood clots or villi. The system was then attached through a strain gauge to another channel of the recorder. The character of the tracing obtained was used as the ultimate criterion that the IVS had been entered rather than any fetal or maternal vessel.

After placement of the catheters they were anchored to the myometrium by a figure-of-eight suture of black silk to prevent slipping. As soon as the recorder stabilized, the abdominal incision was closed with skin clips. At the end of the experiment, after a recording period of from 1 to 4 hours, the skin clips were removed and the catheters withdrawn. The zero base line was checked for each catheter before closure of the abdomen. Postoperatively the animals were given large doses of progesterone (usually about 100 mg. daily for three days) as a protection against abortion due to the procedure.

In all, 57 experiments were performed upon 31 animals. Of these, 9 experiments were eliminated from analysis because they were technically unsatisfactory, reducing the acceptable material to 48 observations upon 30 monkeys. Table I shows the distribution of the observations throughout gestation and the course of the individual pregnancies. The fate of pregnancy over-all is analyzed in Table II. The ratio of 13 pregnancies carried to term versus 17 abortions indicates that repeated operative procedures were reasonably well tolerated. It will be noted furthermore that 5 animals were observed in two successive breeding seasons. All survived and the fates of their pregnancies are shown in Table III.

As seen in Tables II and III immediate and delayed abortion are differentiated. The end of the fourth postoperative day was taken as the dividing point between the two categories since study of the individual records failed to show myometrial evidences of an impending abortion more



than 4 days prior to the event. On the other hand, in any case in which abortion occurred within 4 days, characteristic changes usually appeared in the recording.

TABLE I. RESULTS OF DETERMINATION OF TONUS, AMPLITUDE, AND DURATION OF CONTRACTIONS IN THREE PHASES OF PREGNANCY

MONKEY NO.	DAY OF PREGNANCY	INTERVILLOUS SPACE		AMNION		DURATION OF		SUBSEQUENT COURSE OF THE PREGNANCY	
		TONUS (MM. HG)	AMPLITUDE (MM. HG)	TONUS (MM. HG)	AMPLITUDE (MM. HG)	CONTRACTION (SECONDS)	TONUS (SECONDS)		
A. Preconversion.—									
971	56	10	58			194	50	Live infant	Day 162
977	63			5	55	324	192	Operation	Day 112
9-A	64			5	67	280	247	Operation	Day 119
10-A	64			5	34	252	45	Operation	Day 113
973	66			7	45	300	215	Operation	Day 108
926*	66			5	15	247	110	Abortion	Day 86
11-A	66			2	27	380	231	Operation	Day 115
980	66	4	55	4	34	77	52	Operation	Day 121
16-A	66	4	38	4	33	384	73	Operation	Day 92
909*	68			4	43	196	122	Operation	Day 154
1-A	68	3	29	3	34	234	118	Operation	Day 90
15-A	68	4	28	4	26	323	128	Live infant	Day 116
B. Mid-pregnancy.—									
2-A	71			3	30	293	355	Abortion	Day 85
975	75			2	16	145	106	Abortion	Day 83
926†	87			2	8	303	252	Operation	Day 157
1-A	90			4	17	226	188	Abortion	Day 95
16-A	92			6	33	91	190	Abortion	Day 93
979*	101			1	16	226	249	Operation	Day 124
6-A	101			2	16	125	84	Operation	Day 124
983†	103			2	12	389	76	Abortion	Day 109
4-A	106	4	55	5	36	274	172	Abortion	Day 110
973	108			2	27	175	285	Abortion	Day 111
977	112			5	19	222	271	Abortion	Day 113
10-A	113	5	41	4	30	338	79	Abortion	Day 117
11-A	115			4	16	114	167	Abortion	Day 120
979†	117			4	18	231	289	Abortion	Day 119
7-A	117	3	31	2	21	343	418	Operation	Day 138
L-53	119			4	16	264	184	Operation	Day 140
9-A	119			4	20	250	115	Abortion	Day 121
980	121	6	33	5	29	217	82	Abortion	Day 122
979*	124	2	16	2	19	307	270	Abortion	Day 125
6-A	124			6	16	139	65	Live infant	Day 163
G-41	125			5	19	62	17	Live infant	Day 145
983*	125			4	16	388	74	Abortion	Day 127
3-A	126			4	14	227	170	Operation	Day 148
909†	130			4	17	195	182	Operation	Day 146
L-52†	132			5	34	52	29	Abortion	Day 135
940	135			2	15	123	155	Operation	Day 148
979†	138	4	18	2	17	115	9	Operation	Day 153
C. End of Pregnancy.—									
L-53	140	6	23	4	16	224	71	Live infant	Day 143
8-A	140	6	40	2	26	128	61	Live infant	Day 142
909†	146			6	15	271	289	Live infant	Day 148
940	148	11	38	4	31	102	8	Terminal experiment	
3-A	148	5	32	5	28	346	39	Live infant	Day 149
979†	152	2	42	2	42	670	134	Dead infant	Day 153
L-52*	153	5	21	4	19	225	84	Live infant	Day 156
909*	154			12	44	190	47	Live infant (caesarean)	Day 154
926†	157			4	15	326	287	Live infant	Day 162

\*1958 season.

†1957 season.

TABLE II. FATE OF PREGNANCY IN ENTIRE SERIES OF EXPERIMENTAL ANIMALS

Abortions	17
Immediate	11
Delayed	6
Term Pregnancies	13
Live infants	10
Dead infants	3
Total animals used	30

TABLE III. FATE OF PREGNANCY IN ANIMALS USED IN TWO SUCCESSIVE YEARS

MONKEY NO.	1957 PREGNANCY		1958 PREGNANCY	
	OPERATIONS	FATE	OPERATIONS	FATE
909	4	Living infant	2	Living infant
926	4	Living infant	1	Delayed abortion
983	1	Delayed abortion	2	Immediate abortion
979	3	Dead infant at term	2	Living infant
L52	1	Immediate abortion	2	Living infant

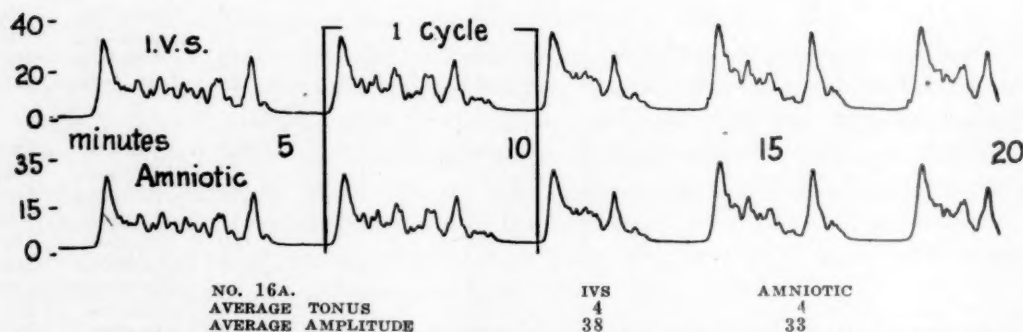


Fig. 1.—Photograph of a simultaneous recording of IVS and amniotic fluid pressures at 66 days. Preconversion.

### Results

**Treatment of Data.**—The “Montevideo Unit” of Caldeyro-Barcia<sup>4</sup> is not a convenient notation of uterine activity in the monkey. It will be remembered that Caldeyro-Barcia calculated the frequency of contractions on the basis of the number of contractions per 10 minutes. In the present studies contractions were often observed to occur 10 or more minutes apart, particularly in mid-pregnancy, so that the Montevideo Unit cannot be usefully employed.

Rather than encumbering the literature with another arbitrary “unit” of limited applicability we have chosen the more tedious but perhaps less confusing method of direct description.

Like Caldeyro-Barcia and others we recognize that each cycle of contraction consists of two elements, a contraction phase and one of relaxation (“tonus”). A cycle is measured, as shown in Fig. 1, from the beginning of the contraction through the following period of relaxation. The contraction phase is considered to be at an end when the level of tonus is regained.

Tonus and amplitude are both measured in millimeters of mercury and amplitude is calculated from zero. (Note that Hellman<sup>6</sup> used millimeters of water and Caldeyro-Barcia<sup>1, 4</sup> expressed amplitude in millimeters of mercury above tonus.) The highest pressure attained in any contraction is taken as the measure of amplitude for that contraction. Planimeter tracings of the recordings were made in the manner and for the reasons described below under “Duration.”

**Findings.**—In Fig. 2 are shown in graphic form the average values of tonus and amplitude and the average durations of the contraction and tonus phases in the series of 48 intrauterine pressure determinations. The exact values are recorded in Table I. The tonus and amplitudes represented in Figs. 2, 3, and 4 are based on amniotic pressures. The relationship between amniotic and IVS pressures in the 16 cases where simultaneous recordings were made is presented in Fig. 5.

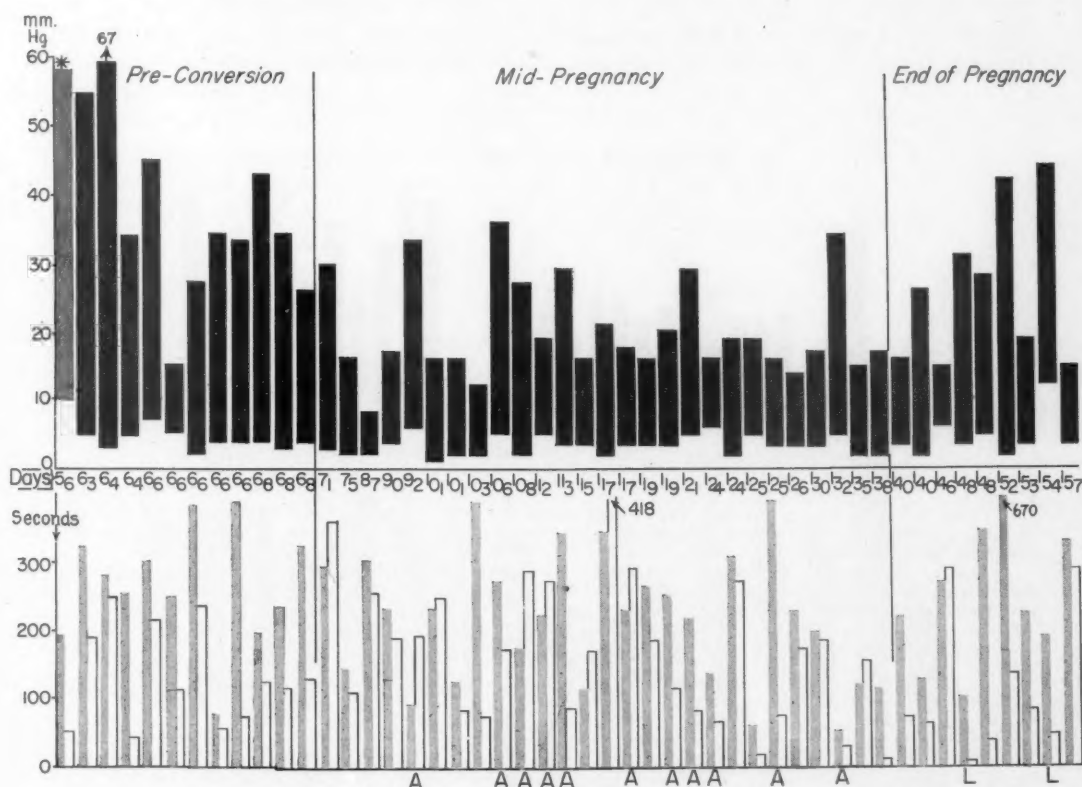


Fig. 2.—Graphic representation of results obtained in determinations of intrauterine pressure at various stages of pregnancy. Above: Solid black bars represent average amniotic pressure values. The lower level of the bar shows tonus; the upper, amplitude. Below: Cross hatched bars show average duration of contraction phase of cycle; white bars, average duration of tonus. Representations of pressure and tonus in a single animal are aligned vertically.

A, Immediate abortion.

L, Active labor.

\*IVS recording alone.

**Amplitude:** From a first glance at Fig. 2 it is apparent that amplitude is high in the preconversion and the end-of-pregnancy periods and tends to be lower in mid-pregnancy. Scrutinizing the chart more closely it will be observed that if amplitude 20 mm. Hg is adopted as a mean, all preconversion values but one lie above it as well as 5 of the 9 cases at the end of pregnancy. On the contrary, only 8 of the 27 mid-pregnancy values lie above 20 mm. Hg, whereas 19 lie below it.

Analysis of the exceptions to this generalization reveals the following circumstances. The one *preconversion* exception is a case in which delayed abortion occurred 20 days after the operation. Some untoward physiological condition was doubtless the cause of the early low amniotic pressure.

If the *mid-pregnancy* cases are separated into those in which immediate abortion occurred and those in which there was no abortion or delayed abortion, it is found that only one of the 8 exceptional cases, i.e., those with amplitude over 20 mm. Hg, occurred in the no abortion group (Fig. 3). This case is that of a 71 day pregnancy in which, although inspection at operation showed the uterus to be cylindrical, the process of conversion was probably still in progress or but recently completed so that some preconversion muscular characteristics persisted. This opinion is strengthened by the fact that no converted uterus was found before the seventy-fourth day of pregnancy in 34 cases previously studied.<sup>13</sup> Therefore, this 71 day case is withdrawn from the statistical calculation of mid-pregnancy conditions.

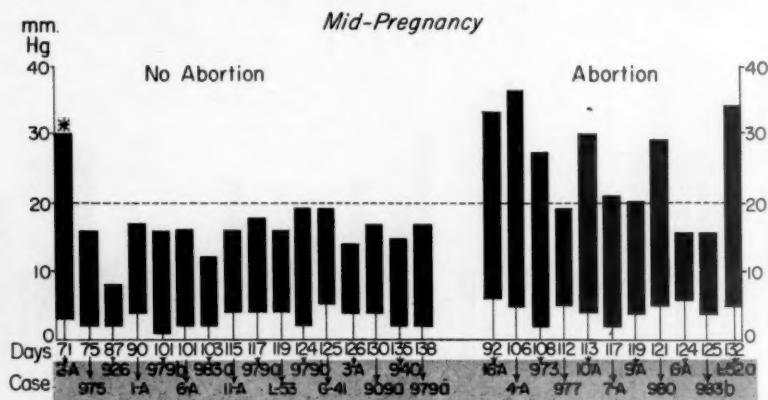


Fig. 3.—An excerpt from the upper part of Fig. 2 showing amplitudes in mid-pregnancy. Cases of immediate abortion are separated from those in which no abortion or delayed abortion occurred. The 20 mm. Hg level is indicated by the broken line.

\*Excluded from statistical analysis. See text under "Amplitude." Lower case letters following specimen number identify specimens used in two experimental seasons. a, 1957 pregnancy; b, 1958 pregnancy.

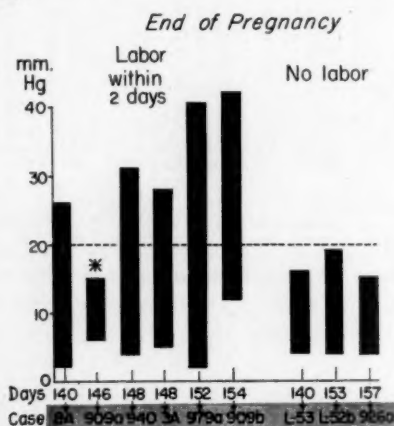


Fig. 4.—An excerpt from the upper part of Fig. 2 showing amplitudes in end-of-pregnancy period. Cases in which labor commenced within 2 days are separated from those in which it did not occur until later. The 20 mm. Hg level is indicated by the broken line. Symbols as in Fig. 3.

The 11 immediate abortion cases, on the other hand, include the 7 other exceptional cases with amplitude at or well above 20 mm. Hg, one case at 19 mm. and 2 in which the amplitude fell appreciably below the mean. The two latter cases are not readily explainable and at present can be interpreted only as expressions of individual variability.

In mid-pregnancy therefore, an amplitude below 20 mm. Hg is the finding to be expected and an amplitude above 20 mm. portends imminent



abortion. The possibility that the immediate abortions in the series were the result of operative manipulation does not affect this generalization. Antecedent operation apparently increased myometrial contractility and the incidence of abortion following the final operation, as indicated by the data presented in Table IV.

TABLE IV. EFFECT OF ANTECEDENT OPERATION UPON FINDINGS AT THE FINAL OPERATION

	AMPLITUDE AT FINAL OPERATION	
	ABOVE 20 MM. HG	BELOW 20 MM. HG
<i>11 Abortion Cases (10 With 2 Operations Each).—</i>		
Antecedent operation	7	3
No antecedent operation	1	0
<i>16 Cases Without Immediate Operation (7 With 2 Operations Each).—</i>		
Antecedent operation	0	7
No antecedent operation	1	8

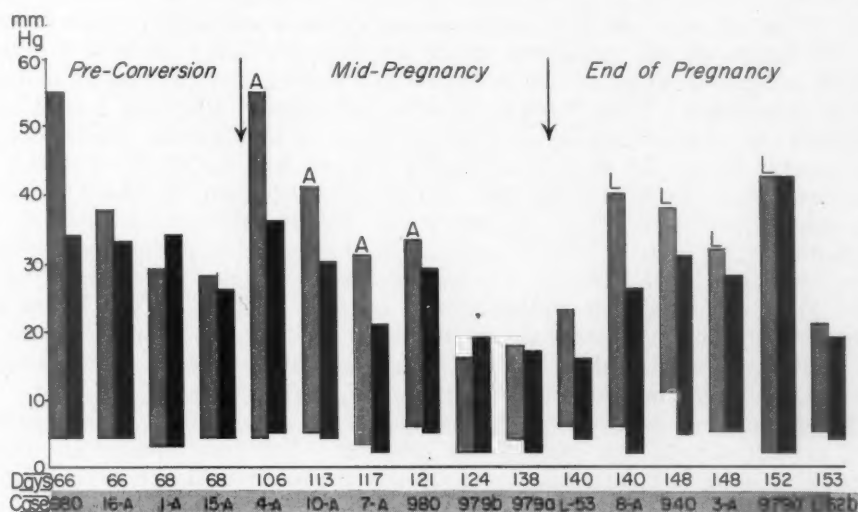


Fig. 5.—Graphic representation of results obtained in cases in which IVS pressure (stippled bars) and amniotic fluid pressure (black bars) were determined simultaneously. Lower level of bars shows tonus; upper level, amplitude.

A, Immediate abortion.  
L, Labor within 2 days.  
Symbols as in Fig. 3.

If the 9 cases falling in the *end-of-pregnancy* period are divided on the basis of time of onset of labor, it is found that in 6 cases labor commenced either during the operation or within 48 hours. In all of these except one the amplitude markedly exceeded 20 mm. Hg. The remaining 3 cases in which labor did not commence for 3 to 5 days showed amplitudes between 15 and 20 mm. Hg. In the one exceptional case of the "labor" group (No. 909 in the 1957 season) the operative procedure involved extensive manipulation after the recording of uterine pressure was completed. Because of this the case is excluded from the statistical analysis. Thus, the generalization holds that end-of-pregnancy cases have amplitude in excess of 20 mm. Hg when labor is in progress or imminent.

In summary, despite the exceptions noted in each period of pregnancy, the initial impression that mid-pregnancy is normally a period of low

amplitude is confirmed by closer study. Simple inspection shows the close similarity of amplitudes at the two ends of pregnancy and statistical analysis shows that the differences between average amplitudes at the three periods of pregnancy have a high degree of significance as between preconversion and mid-pregnancy and as between mid-pregnancy and labor (Table V).

TABLE V. AVERAGE AMPLITUDE BASED ON AMNIOTIC PRESSURE VALUES IN MM. Hg

	N	MEAN	STANDARD DEVIATION	t	P
Preconversion	11	38	$\pm 13.7$	5.8	< 0.01
Mid-pregnancy	15	16	$\pm 2.6$		
End of pregnancy (labor only)	5	34	$\pm 7.4$		

**Tonus:** The average values for tonus fall between 1 and 6 mm. Hg in all stages of pregnancy, except in one case in active labor (909 in the 1958 season, 12 mm. Hg).

**Duration:** Less informative than the data on amplitude are those on the duration of the contraction and tonus phases of the contraction cycle (Fig. 2). The major trend which manifests itself is that one-third of mid-pregnancy cases show preponderance of tonus over contraction, the reverse relationship prevailing otherwise. This feature of mid-pregnancy, like the lower amplitude, reflects the diminished myometrial activity of this period when placental progesterone is in ample supply. Similar preponderance of the tonus phase was observed only once outside the mid-pregnancy span, in the exceptional prelabor case mentioned above (Monkey No. 909 in 1957 at 146 days). It is further noteworthy that the high amplitude characterizing the preconversion period is associated with longer contraction cycles than those which accompany the high amplitude of prelabor and labor. Indeed, in the latter state cycles are very brief and tonus is strikingly curtailed. Thus absolute and relative durations of the phase provide ancillary information on the state of activity of the uterine musculature (Figs. 1, 6, 7, and 8).

This relationship can be well visualized if the recordings of intrauterine pressure are measured by planimeter tracing. By this means the square millimeters of area between the level of the pressure and the zero base line can be accurately determined. The value so derived reflects both the influence of duration of contraction and tonus in the constitution of the cycle of contraction and also the influence in the total contraction effort of secondary peaks. Amplitude data (Figs. 2-5) ignore the later. It should be recognized that the square millimeter values obtained by planimetry are not in point of fact units of energy but are significant only as comparative measures of myometrial activity. As such, planimetric measurements confirm the relative quiescence of mid-pregnancy contrasted with the activity of preconversion and end-of-pregnancy and make clear that preconversion contractions, although often characterized by amplitude as high as that of labor, exert less force per given unit of time than the latter by virtue of generally longer cycles and longer periods of tonus.

**Intervillous space versus amniotic pressures:** Simultaneous recordings of IVS and amniotic fluid pressures were made in 16 cases as shown in Table I and graphically represented in Fig. 5. Average amplitude of IVS pressure in 13 cases was 35 mm. Hg while that of the amniotic pressure in the same cases was 27 mm. Hg. In one case amniotic and IVS pressures were equal. In only 2 cases was the amniotic pressure higher than the IVS pressure. One case was from the preconversion period, the other from mid-pregnancy.

Tonus and amplitude values and duration of tonus and contraction marked these cases as perfectly typical of their respective groups. The excess of the amniotic pressure over the IVS was less than the usual excess of IVS over amniotic which was frequently of pronounced magnitude. Similar variation in the relationship of IVS and amniotic pressures is recorded in the, as yet, sparse literature on the subject. Caldeyro-Barcia<sup>1, 4</sup> reported uniform predominance of IVS pressure, Hellman,<sup>6</sup> in 8 cases, predominance of amniotic pressure in 5, and Prystowsky<sup>10</sup> uniform predominance of IVS pressure at the height of contractions. Hendricks<sup>7</sup> reported "virtually identical" pressures in the amniotic fluid space and the IVS during labor. All made their observations in humans.

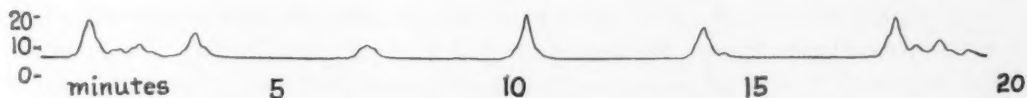


Fig. 6.—Photograph of a recording of amniotic fluid pressure at 130 days. Mid-pregnancy. No. 909, 1957 pregnancy. Average tonus, 4; average amplitude, 17.

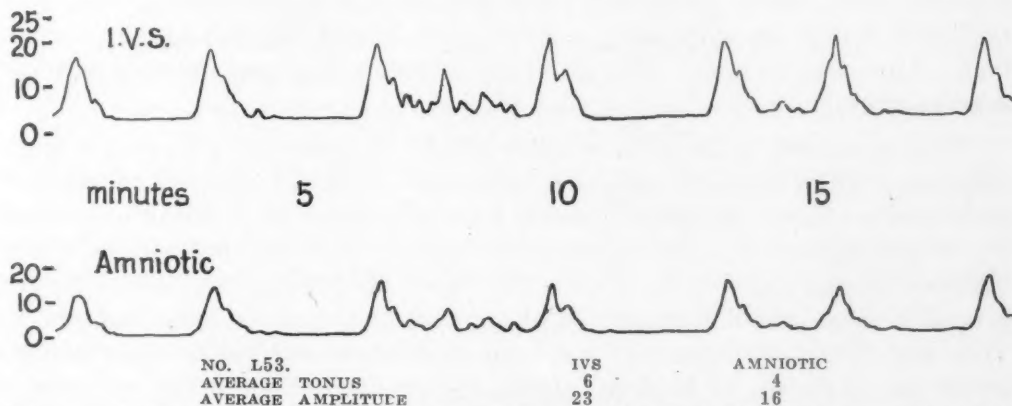


Fig. 7.—Photograph of a simultaneous recording of IVS and amniotic fluid pressures at 140 days. End of pregnancy.



Fig. 8.—Photograph of a recording of amniotic fluid pressure during labor. No. 940 at 148 days. Average tonus, 4; average amplitude, 31.

The alternation in the relationship of intervillous space and amniotic pressure, however, is of little consequence in comparison with a more important consideration, namely, the spread between highest intrauterine pressure, wherever found, and maternal arterial pressure. Even the highest average IVS pressure of 58 mm. is well removed from the systemic arterial blood pressure of the monkey (135/85) as determined by direct intra-arterial recordings in 12 monkeys prior to pregnancy. Simultaneous determinations of uterine blood pressure and intrauterine pressure are in progress in a further series of rhesus monkeys, but it is already apparent that the differential favors unimpeded flow from maternal artery to IVS and from IVS to maternal vein, save when the latter is occluded by myometrial contraction.

Study of the time of onset of contraction and tonus in the IVS and amniotic cavities, respectively, shows no consistent difference. In the course of a single recording the lead may alternate between the two cavities or be simultaneous. The lead was never in excess of 0.8 second.

### Comment

Two facets of placental circulation are illuminated by the present data: the levels of pressure within the maternal placenta of the monkey at successive stages of pregnancy; and the effect of uterine contraction upon placental drainage.

It is the testimony of 11 normal preconversion, 15 mid-pregnancy, and 5 labor cases that 20 mm. Hg is the normal average amplitude. If that pressure is exceeded in conjunction with short cycles in which contraction time exceeds the duration of tonus, the characteristic pattern of preconversion can be recognized. If the cycles are yet further curtailed and the tonus intervals are very brief, labor, prelabor, or preabortion periods can be diagnosed. In the latter conditions amplitude may rise to 45-70 mm. Hg although 20-45 mm. is the more common range. The similarity of preabortion and prelabor patterns is noteworthy.

The increased myometrial activity at the two ends of pregnancy (high amplitude, short cycles) coincides with the repeated finding of relative progesterone deficiency in the periods when the placenta is taking over from the corpus luteum in early pregnancy and when placental production of the hormone wanes just before labor. The work of Bieniarz and Reynolds<sup>3</sup> in pregnant ewes provides experimental support of the views expressed above. They find that disturbances of maternal circulation, elicited by vagal stimulation and injection of humoral mediators, produce either active or passive engorgement of the placenta and that this obstruction of the uteroplacental circulation is associated with increased intrauterine pressure. As previously noted, the present study indicates that such disturbances appear physiologically at times when lowered blood levels of progesterone permit more active myometrial contractility and more frequent and prolonged venous occlusion.

These times of increased activity coincide with periods of pronounced circulatory embarrassment as previously described by others.<sup>15, 18</sup> The initial premise of the present study, that myometrial contractions throughout pregnancy enhance circulation, is not invalidated by this apparent contradiction. The same action which in its mild form in mid-pregnancy (Fig. 6) helps to clear the placental pool of blood causes actual stasis when exaggerated (Figs. 1 and 8). The work of Woodbury<sup>17</sup> and the conclusions he drew from his data harmonize with this opinion of the effect of moderate myometrial activity, and his study of the effect of oxytocics<sup>16</sup> supports the concept of circulatory impairment in the presence of excessive uterine contractility. Recent uterine circulation studies by Assali,<sup>2</sup> Metcalfe,<sup>8, 9</sup> and Hendricks<sup>7</sup> confirm Woodbury's original findings showing that a uterine contraction first



washes blood from mural uterine veins into the maternal systemic channels and subsequently, at the peak of the contraction, traps blood in the placental pool. At the peak, maternal systemic arterial and venous pressures are both slightly elevated and cardiac output drops sharply as the contraction wanes, doubtless as the result of blood flowing back into the reopening channels.

### Summary

1. In 30 pregnant rhesus monkeys 48 determinations of intrauterine pressure were made. In 16 of the experiments both intervillous space (IVS) and amniotic fluid pressures were determined.

2. In preconversion and end-of-pregnancy periods amplitude was normally above 20 mm. Hg. In mid-pregnancy the amplitude was below 20 mm. Hg, rise of amplitude above this level foreshadowing imminent abortion.

3. Contraction cycles were longer in mid-pregnancy and in one-third of the cases tonus predominated over contraction. Shorter cycles with predominance of the contraction phase characterized preconversion. Still shorter cycles with very brief periods of tonus were typical of the prelabor, labor, and preabortion periods.

4. Intervillous space pressures were higher than amniotic fluid pressures in 13 of the 16 cases of simultaneous recording. The average IVS pressure of 35 mm. Hg was 100 mm. lower than average maternal arterial systolic pressure, however, and 50 mm. lower than the diastolic. This differential favors unimpeded flow of blood from maternal artery to IVS and from IVS to maternal vein, save when the latter is occluded by myometrial contraction.

We wish to express warm gratitude to Dr. Bent G. Böving for advice and assistance in analysis and interpretation of the data.

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## PRESSURE RELATIONSHIPS BETWEEN THE INTERVILLOUS SPACE AND THE AMNIOTIC FLUID IN HUMAN TERM PREGNANCY\*

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THE fetal "atmosphere" in utero is fluid, and consists of (1) the amniotic fluid, and (2) the maternal blood in the intervillous space. The intervillous space must be considered a legitimate part of the fetal "atmosphere" because it impinges directly upon a large fetal structure, the placenta, which in turn transmits pressure into the amniotic sac, principally through acting upon the large component of the fetal circulation which is coursing through the placenta.

In extrauterine existence, a rise in the atmospheric pressure brings about a rise in human blood pressure by an equivalent amount, thus preserving a constant pressure relationship between man and his environment. The classical example of the skin diver illustrates the point. As the diver swims deeper and deeper, the pressure surrounding him becomes progressively greater. Within limits, his blood pressure remains "stable" in its relationship to the pressure existing in the water at any given depth; the stability is brought about by an increase in the blood pressure by the same amount that the water pressure at any given depth exceeds the pressure of the air at the surface. Thus at a depth of 30 feet, for example, the skin diver is definitely "hypertensive" if his blood pressure is taken in reference to the atmospheric pressure at the surface, but he will remain "normotensive" when his pressure is referred to that of the water which surrounds him.<sup>1</sup>

The consistency of the relationship between the two fluid compartments of the fetal "atmosphere" is a matter of vast importance to the fetus. When the uterus contracts, the fetal blood pressure rises as much as the rise in amniotic fluid pressure,<sup>2</sup> thus keeping constant the pressure gradient between the fetus and that part of his environment. But the total fetal environment is not being maintained unless the rise in amniotic fluid pressure is closely paralleled by an equivalent rise in the pressure of the intervillous space.

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It has been observed by Alvarez and Caldeyro-Barcia<sup>3</sup> that the amniotic fluid pressure and the intervillous space pressure in the human are about equal at any stage of the contraction cycle.

Hellman, Tricomi, and Gupta,<sup>4</sup> however, making simultaneous readings of the two spaces with water manometers, found that while there were frequent changes in the amniotic fluid pressure, "the intervillous pressure, on the other hand, appeared more stable, and was less quickly and directly affected by uterine motility. It was surprising," they reported, "how often this latter pressure was less than the amniotic fluid pressure." In their 8 cases in which they listed the "average resting levels" of these pressures, 5 of the amniotic fluid pressures (converted to millimeters of mercury) exceeded the intervillous space pressures by 21.1, 6.7, 11.1, 2.6, and 4.9 mm. Hg, respectively. In the remaining 3 cases, the intervillous space pressures exceeded those of the amniotic fluid pressures by 2.5, 5.2, and 2.6 mm. Hg, respectively. When they injected 1 I.U. of Pitocin intramuscularly and then sought the maximum pressures achieved during the resulting uterine contractions, they found that in all 3 cases the amniotic fluid pressure exceeded the intervillous blood pressure, by the amounts of 6.6+, 12.0, and 3.7 mm. Hg, respectively.

Prystowsky,<sup>5</sup> making individual pressure observations on 12 patients as a part of his larger project of fetal blood studies, found that in the resting uterus the average of the intervillous space pressures (9.8 mm. Hg) exceeded the average of his amniotic fluid pressure observations (7.4 mm. Hg) by 2.4 mm. Hg. The averages of the intervillous space pressure and the amniotic fluid pressure when the uterus was contracting, however, were 38.2 and 18.7 mm. Hg; thus the average intervillous space pressure exceeded the average amniotic fluid pressure by 19.4 mm. Hg. In the 2 cases where both spaces were measured in the same individual in the "resting uterus," he found that in one instance the amniotic fluid pressure (3.5 mm. Hg) exceeded the intervillous space pressure (3.2 mm. Hg) by only 0.3 mm. Hg, while in the other case the intervillous space pressure (19.8) exceeded the amniotic fluid pressure (4.4) by 15.4 mm. Hg. In the case where both pressures were measured in the contracting uterus of the same individual, the intervillous space pressure (38.2 mm. Hg) exceeded the amniotic fluid pressure (15.5 mm. Hg) by 22.7 mm. Hg.

While both of the above series were admittedly small, there is nothing in the reports which indicates any particularly systematic relationship between the pressures in the two spaces.

The present paper reports studies conducted to determine the nature of the pressure alterations which take place in the intervillous space (IVSP), and of the relationship of these pressure alterations to alterations in the amniotic fluid pressure (AFP).

### Material and Methods

Studies conducted on 7 human subjects at term form the basis of this report. All were either in labor or had been admitted to the hospital for induction of labor. Hundreds of contraction cycles were studied. Because the



recordings were being made continuously, usually for a number of hours, it was possible to observe each patient under a variety of changing conditions, such as before and during caudal analgesia and before and after the administration of sedatives. There were also observed the effect of oxytocin infusion, the effect of rupture of the membranes, and the effect of movements of the patients. In 3 of the subjects, a single soft-tissue x-ray study was made the day before admittance to determine localization of the placenta. In the remaining 4 subjects, the IVS was entered during a scheduled catheterization of the amniotic fluid cavity for other studies. (It had been previously agreed that should such an inadvertent entry take place, the catheter would be left in situ and the pressure of the maternal blood in the IVS would be recorded.) Several other subjects were screened for this study but proved unsuitable because x-ray studies indicated that the placenta was located posteriorly. Two additional patients early in the series were eliminated from the study because of failure to obtain a sufficiently long record for satisfactory evaluation.

The amniotic cavity was catheterized by the method of Alvarez and Caldeyro-Barcia,<sup>6</sup> the only significant variation being the use of No. 17 gauge Touhy needles instead of the larger straight trocar type needles employed by Alvarez and Caldeyro-Barcia. The same technique was used for entering the IVS. Upon penetration of the IVS, free blood appeared in the needle under some pressure, the amount of backflow being determined by the state of contraction of the uterus at the moment. Through the needle, about 20 cm. of polyethylene catheter was threaded into the IVS and left in place while the needle was withdrawn.

Besides the evidence cited above, further evidence was obtained to indicate that the catheter was in the IVS in 3 of the cases where, after delivery and manual removal of the placenta the catheter, which had been left in place during delivery, was demonstrated to be lying free in the placental bed.

The catheter was flushed at frequent intervals throughout the duration of the study because, while the blood flows freely at the initial tapping, the high degree of coagulability of the blood in the IVS predisposes the system to "damping" after a certain length of time, and eventually to total obstruction by clot.

The flushing was carried out with a rather heavily heparinized (40 mg. per 500 c.c. sterile saline) solution, the "flush" periods usually occupying very little time, being often almost instantaneous. If the testing system is perfectly sealed, as it must be to make accurate recordings, the intervillous pressure can be successfully recorded for many hours while only a scant amount of the heparinized solution is introduced.\*

The AFP and the IVSP were transmitted through Sanborn manometers. In the study described later, a differential pressure manometer was also employed in order to obtain simultaneous and continuous records not only of both the AFP and the IVSP but, on a third channel, of the difference between these pressure values. All results were traced on Sanborn multiple channel recording equipment.

## Results

*1. The Nature of the IVSP Wave.*—The pressure alterations developed in the IVS during uterine contractions appear to be of the same form as the alterations brought about in the AFP by the contraction cycles. Fig. 1 consists

\*One milliliter of this solution contains only 0.08 mg. of heparin. At a steady flushing pressure of 200 mm. Hg 1 ml. passes through the catheter in 20 seconds of continuous flushing. In the more nearly instantaneous flushes, which were usually employed, approximately 40 flushing procedures can be carried out before a full milliliter of the flush solution is introduced into the IVS. Often a full hour of recording was carried out during which no more than 1 ml. of the solution was used. When this amount (0.08 mg.) is compared with the usual therapeutic range of single intravenous dosage (50-100 mg.), it may be seen that there are practically no dangers of complications from the use of the heparinized solution.



of IVSP tracings from 4 different subjects. All these tracings, as well as all other tracings obtained, appeared to have the typical response which is observed in the AFP, namely, a rapid increase in pressure until the apex of the contraction is attained, followed by a progressively slowing decline in pressure during the balance of the contraction cycle.

2. *Direct Comparison Between AFP and IVSP During Contractions.*—In Fig. 2 there is shown a photograph of one subject's IVSP tracing (line *a*) and her AFP tracing (line *b*). In line *c*, a transparency taken from the ISVP tracing is superimposed upon the AFP photograph. It may be noted that there are almost no detectable differences between the two tracings. A similar study is illustrated from another subject in Fig. 3; in this instance a small discrepancy appeared, the AFP tending to exceed the IVSP during a portion of uterine systole. The general shape of the two curves, however, remains unaltered.

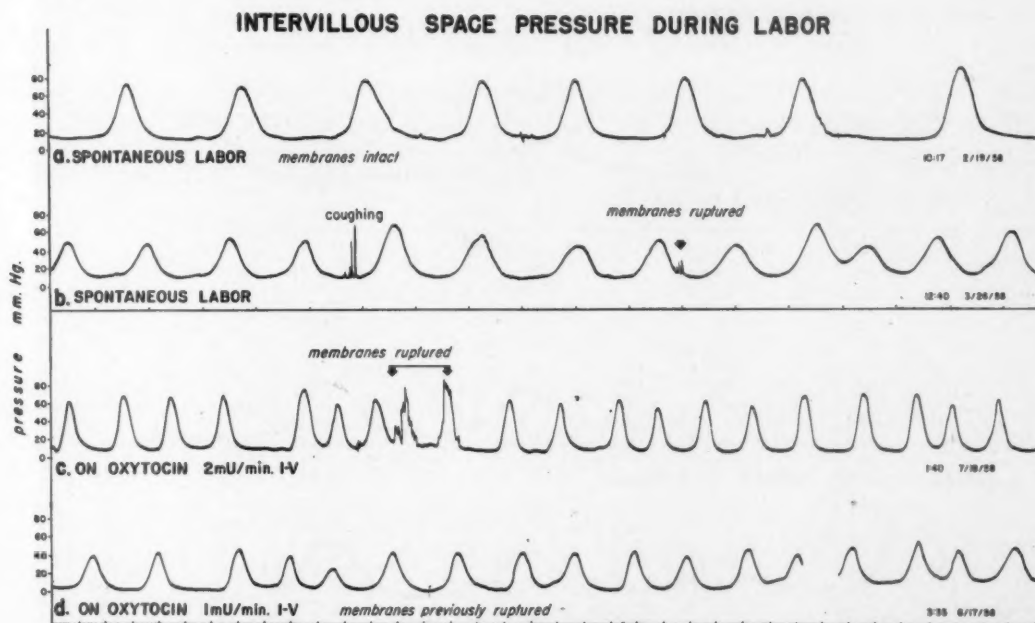


Fig. 1.—Tracings of the intervillous space pressures from 4 different human subjects during labor. (Note that the upper 2 records were made at twice the speed of the lower 2 records. Ticks under the second and fourth lines designate minutes.) The pattern of the intervillous space pressure is indistinguishable from the pattern of the amniotic fluid pressure changes in labor, whether the labor is spontaneous or induced, and whether the membranes are intact or ruptured. Pressure increases brought about by coughing or bearing down at artificial rupture of the membranes may be clearly seen in lines *b* and *c*.

An additional study was made to bring out more detail of the relationship between the two spaces under consideration. While the AFP was being traced in Channel *a* (Fig. 4), this fluid system was at the same time connected to a differential pressure manometer, and transmitted to Channel *c* as a *positive* pressure. The IVSP system, which was being traced in Channel *b* was also connected to the differential pressure manometer, but transmitted to Channel *c* as a *negative* pressure. Thus it was possible to make a continuous record of the pressure relationships between Channels *a* and *b*. When the differential pressure scale was at all comparable in magnitude to the scales being used to record the AFP and the IVSP, the differential pressure differences ( $A - B$ ) appeared slight and ill defined. In the left half of Fig. 4, where the differential pressure scale is only 1.25 times the scale being employed in Channels *a* and *b*, there is no clearly evident difference between the two pressure systems. When

the scale of Channel *c* is doubled (to 2.5 times that of *a* and *b*), as seen in the right half of Fig. 4, a consistent pattern of pressure differences begins to become evident; while the AFP and the IVSP remain essentially identical in uterine diastole, with the onset of a uterine contraction there is a consistent small rise in Channel *c*, indicating that the AFP is greater than the IVSP.

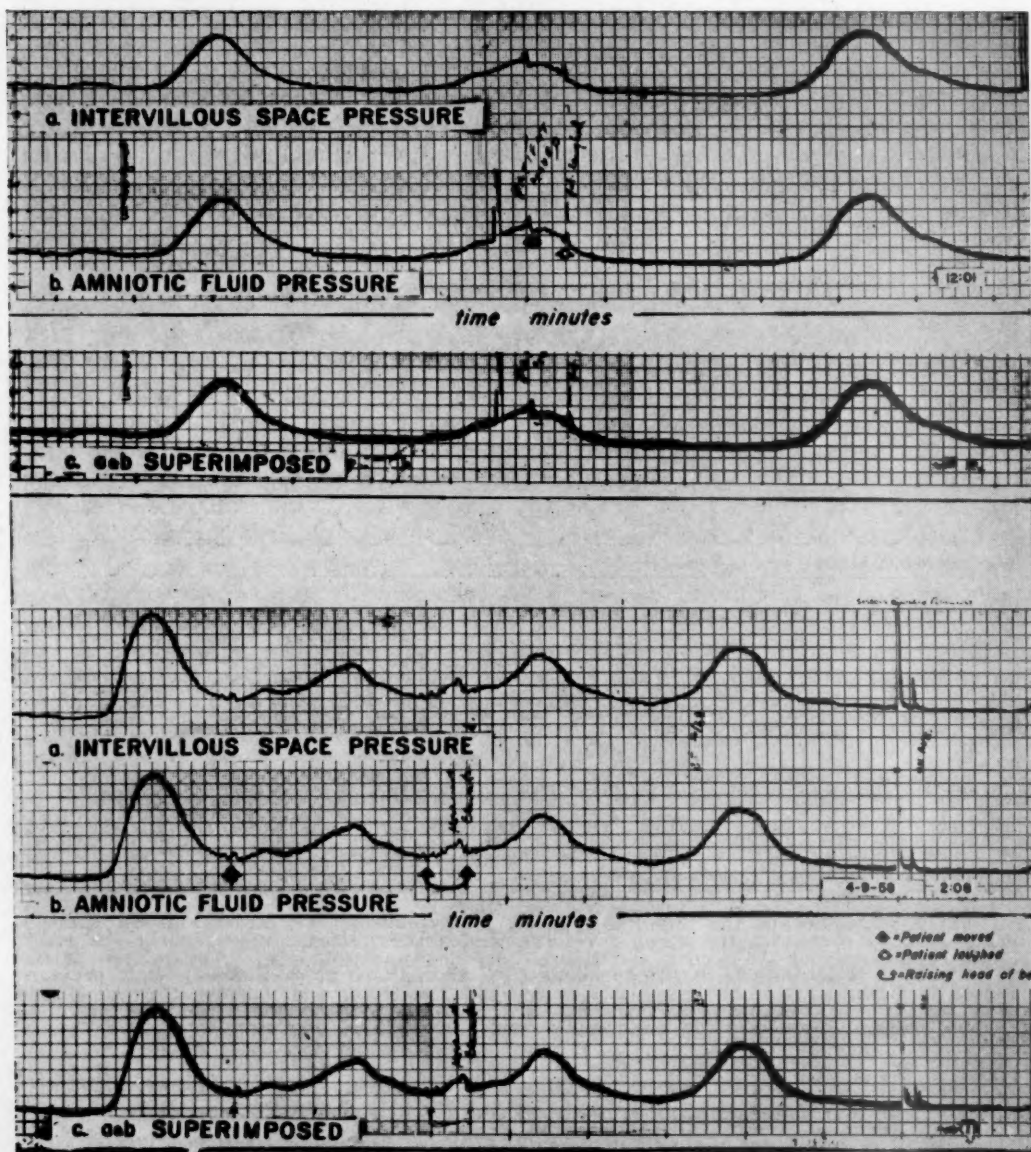


Fig. 2.—Simultaneous study of the IVSP and the AFP. When the IVSP tracing (line *a*) is superimposed over the AFP (line *b*), the result (line *c*) forms a continuous line indicating that the pressures are very nearly identical throughout the length of the tracing. As illustrated, the pressures remained essentially the same even when the subject moved, laughed, or was having the head of her bed raised.

When the scale of Channel *c* is expanded to approximately 12.5 times that of Channels *a* and *b*, the pattern becomes still clearer (Fig. 5). In the very early part of uterine systole the AFP begins to exceed the IVSP by a small amount, this difference increasing quite rapidly as systole develops until 8 to 10 seconds before the apex of the contraction, at which time the AFP exceeds the IVSP by

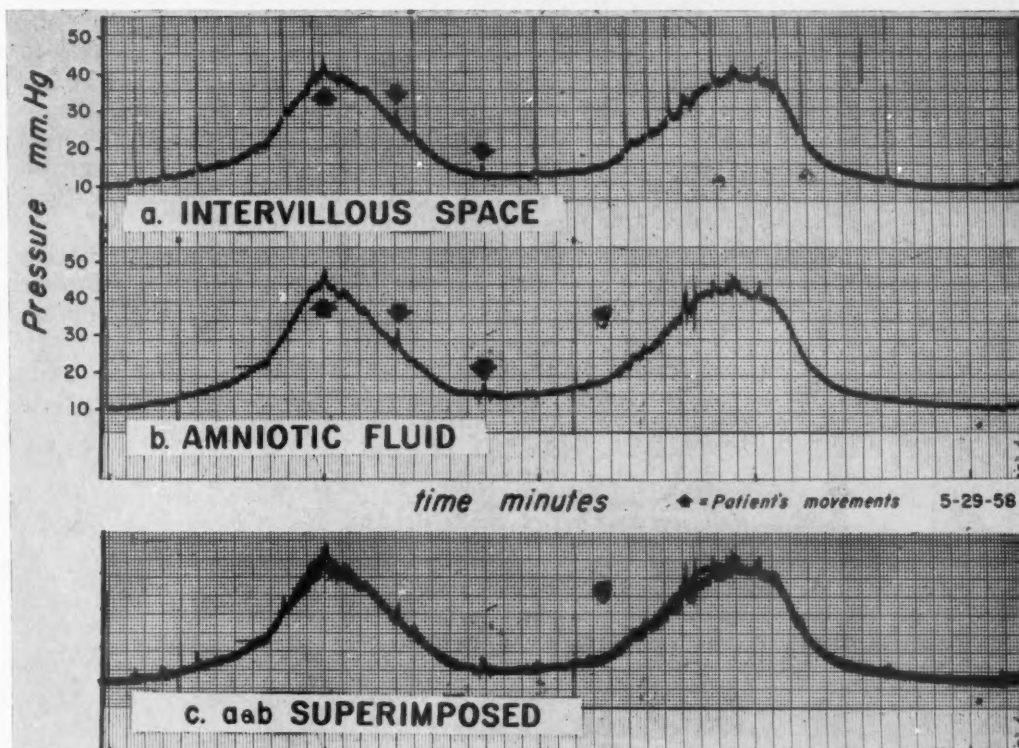


Fig. 3.—Simultaneous study of the IVSP and the AFP. In this record, the procedure was the same as that of Fig. 2, but in this subject the AFP slightly exceeded the IVSP during the first half of the contraction cycle. The black arrows in lines *a* and *b* designate points at which the subject moved. As shown in line *c*, the alterations brought about by movement of the patient were very nearly equal in amount and simultaneous in time.

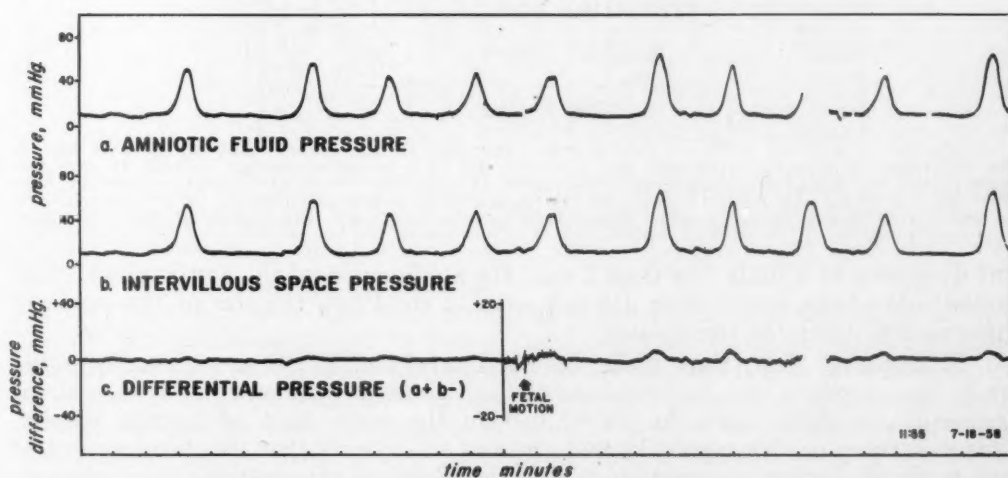


Fig. 4.—Differential pressure study (see text). By introducing the pressure values of the AFP (line *a*) and of the IVSP (line *b*) as positive and negative forces, respectively, into a differential pressure recording (line *c*), it was possible to record the value of (AFP minus IVSP). The difference is not notable in the left-hand side of the chart, when the scale of line *c* was only 1.25 times the scale of lines *a* and *b*. When the scale of line *c* was doubled, there could be noted a rather consistent small rise in the AFP over the IVSP beginning with the early part of the contraction cycle.



approximately 2.5 mm. Hg. By the time the apex of the uterine contraction is reached, the difference between the two pressures is already declining (i.e., the IVSP is "catching up" with the AFP), and this difference subsides further to near zero during uterine diastole.

After demonstration that with sufficient magnification of the scale a small difference between the AFP and the IVSP can be shown, it is interesting to note the small inset in the upper right-hand corner of Fig. 5, which is the photograph of the AFP tracing superimposed upon the IVSP tracing in this illustration. At the original scale, the two tracings appear to coincide very well.

In a large number of contractions in which the AFP intensity ranged from 34 to 61 mm. Hg over the tonus level, the transient dominance of the AFP over the IVSP ranged from 1.6 to 3.2 mm. Hg, averaging 2.6 mm. Hg at its maximum,

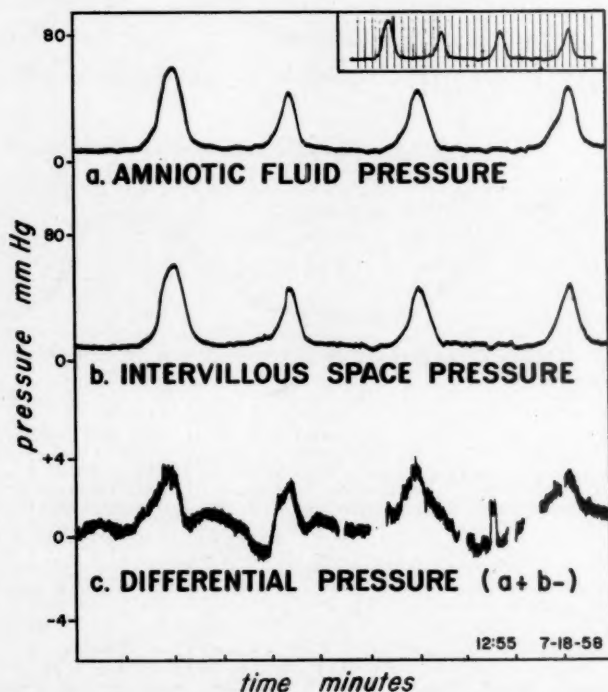


Fig. 5.—When the scale of line *c* was expanded to 12.5 times that of lines *a* and *b*, the difference in pressures between the AF and the IVS becomes clearer. Eight to ten seconds before the apex of a contraction, the AFP exceeds the IVSP by approximately 2.5 mm. Hg. In the upper right-hand corner of the figure is a small photograph of a superposition of line *a* over line *b*, showing what appears to be a satisfactory coincidence of the 2 tracings.

but dropping to a little less than 2 mm. Hg at the apex of the contraction. The magnitude of the contraction did not seem to condition the size of the pressure difference between the two spaces.

It appears, then, that while the AFP and the IVSP are virtually equal when the uterus is not actively contracting, there is a very small transient increase of the AFP over the IVSP during the early part of uterine systole. This difference occurs regularly and appears to indicate that the development of full pressure with a contraction is slightly faster in the amniotic fluid than in the intervillous blood.

### 3. The Effect of Increasing Abdominal Pressure, and of Fetal Movements.—

Numerous instances were found during the course of the study in which the subject either voluntarily or involuntarily altered the intra-abdominal pressure, as shown in the figures. In Fig. 1, *b* there is shown the sharp response of the IVSP



to coughing by the subject. Figs. 2 and 3 illustrate that the AFP changes induced by the patient's movement or laughter, or by elevating the head of the bed were quite accurately reflected by equivalent changes in the IVSP. Fig. 6 shows additional examples of the closeness of the response in the two spaces to the subject's raising her knees, getting on and off the bedpan, and straining down at the time of vaginal examination.

It was also of interest to note that the AFP response to fetal movements was usually paralleled by approximately equivalent changes in the IVSP.

4. *The Effect of Rupture of the Membranes.*—In Fig. 1, there are illustrated segments of the IVSP records of 4 subjects. In line *a* the membranes remained intact, while in line *d* they had been previously ruptured. In lines *b* and *c* the record was continued during artificial rupture of the membranes. Whether

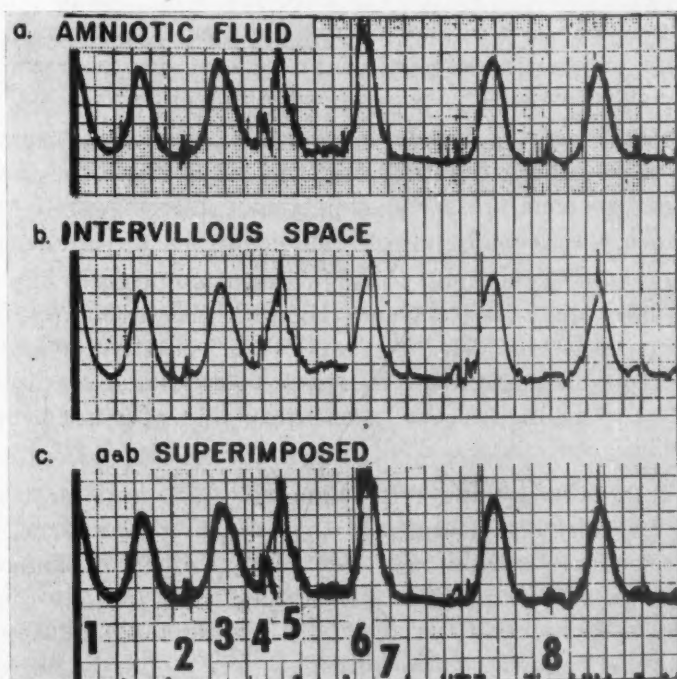


Fig. 6.—The effects of movement and amniotomy upon AFP and IVSP. The numbers at the bottom of the illustration correspond to the following notes: (1) subject in supine position, (2) raising knees in preparation for examination, (3) vaginal examination, (4) pressure applied to fundus during amniotomy, (5-6) subject pushed with contraction, (7) off bedpan, (8) listening to fetal heart.

or not the membranes had been ruptured appeared to have no visible effect on the IVSP, which continued to follow the typical AFP curve. Detail study of the AFP-IVSP relationship during amniotomy in Fig. 1, *c* is presented in Fig. 6, where it may be seen that the pressures in both spaces followed a similar course during the amniotomy and, in spite of numerous extraneous influences, the normal uterine contractility pattern continued. In the cases illustrated the amniotic fluid was permitted to come away slowly. It would have been a matter of much interest to observe whether any larger difference in pressure might have appeared if the amniotic fluid had been withdrawn suddenly.

5. *The Effect of Oxytocin.*—In subjects who were receiving constant infusions of synthetic oxytocin within physiologic dosage, there was no demonstrable difference between the AFP and the IVSP. The current study did not

include the study of any single injections of oxytocic substances, inasmuch as we were interested solely in studying physiologic rather than pathologic conditions.

### Comment

It has been shown that the IVSP responds in almost the same fashion as does the AFP to alterations in intrauterine pressure, whether the alterations are brought about by myometrial contractility or by a force acting to increase the intra-abdominal pressure.

Neither the IVSP nor the AFP alone may be considered as a "stable" mechanical pressure state, inasmuch as each is constantly responding to the dynamically evolutionary process of the uterine contraction cycle. On the contrary, the AFP and the IVSP remain consistently "stable" in relationship to each other, as one contraction follows another. It becomes evident that this beautifully ordered relationship may be best demonstrated through the continuous recording of both parameters simultaneously.

Thus it would not be grossly inaccurate to use the term "intrauterine pressure" to include both the AFP and the IVSP, since the uterus acts as a moderately homogeneous pressure compartment, offering the fetus a complete atmosphere which is reasonably uniform under physiologic conditions.

There still remains the knotty problem of attempting to explain the small and transient difference of about 2 mm. Hg which begins to appear in the early portion of the contraction cycle. A number of speculative possibilities present themselves. All of the possibilities mentioned below must presuppose a certain small amount of resistance to the transmittance of pressure between the two compartments involved:

1. Something done by the fetus himself. This is a most unlikely possibility, since any absolute changes in the fetal blood pressure, for example, even if they occurred, should not affect the IVSP-AFP changes in such a rhythmic response in the differential pressure. In fact, if the fetal blood pressure dropped suddenly to zero, it still should not make any immediate difference in the AFP-IVSP relationships.

2. Local progesterone dominance of the myometrium over the placental site, as indicated by Csapo.<sup>7</sup> It might be argued that the myometrium contracts sooner and with greater efficiency about the amniotic sac, thus producing a more rapid rise in AFP than occurs in the IVSP.

3. Variations in the flow state and volume within the intervillous space. This is perhaps the most complex of the possibilities. At the onset of a contraction the intervillous space has both arterial input and venous outflow in operation. With early increases in pressure, there is a rapid extrusion of a portion of the blood in the intervillous space. Then, as the contraction gains intensity, the venous outflow stops, and the arterial input continues but at a decelerating rate. Presupposing a small amount of resistance in the membrane between the two compartments, one might hypothesize that, because of the free outflow of part of its contents during the early part of the cycle, the IVSP tends to be a bit below that of the AFP. After the venous shutoff, as

arterial blood continues to be pumped into the IVS, the IVSP "gains" on the AFP until eventually the pressures come into equilibrium. A rise in maternal blood pressure during the contraction should contribute to the speed with which this pressure differential is obliterated.

Because of the consistency of the small pressure differential between the AFP and the IVSP, it seems only logical that small differences in the pressures of the two spaces might result from various local disturbances. Further studies of such factors by the differential pressure method should help to establish these differences, and to shed new light on the processes by which the fetus is enabled to adapt to unpredictable difficulties in intrauterine existence.

It should be emphasized that the principal finding of this study is *not* the differences between the amniotic fluid pressure and the pressure in the intervillous space, but rather the degree to which these pressures respond in similar fashion both to uterine contraction cycles and to extrauterine influences. The fact that it was necessary to "expand" the differential pressure scale greatly to make the differences appear speaks strongly for the near identity of the pressures in the two spaces.

### Summary

1. The intervillous space and the amniotic fluid pressures were recorded simultaneously and continuously for prolonged periods of time.

2. As long as the uterus is not in active systole, the pressures in the two spaces remain virtually identical.

3. Recording on a sensitive scale the pressure difference between the intervillous space and the amniotic fluid shows that during uterine systole the amniotic fluid pressure increases slightly faster than does the pressure in the intervillous space, the average maximum differential being approximately 2.6 mm. Hg. This pressure differential is partially "erased" by virtue of the fact that the pressure in the intervillous space makes up part of the pressure deficit by the time the apex of the contraction is reached.

4. Movement of the patient brings about alterations in the pressure of approximately equal amounts in both spaces, and without appreciable lag. The amniotic fluid-intervillous space pressure relationship seems to be unaffected by either rupture of the membranes or the administration of oxytocin in physiologic dosage.

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## ALTERATIONS IN BODY COMPOSITION DURING PREGNANCY\*†

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THE proportions of water, pure fat, and fat-free solids in the human body are variable.<sup>1, 8, 9, 16, 18, 19-21, 25</sup> The estimation of these gross constituents in the living individual by means of densimetric and hydrometric techniques constitutes a significant development in the study of human biology in general and of water and electrolyte metabolism in particular.

Data concerning the gross body composition of normal men and women, which have been obtained by the use of these methods, indicate that the variability in water content of the human body, which is evident when this component is related to body weight, is approximately inversely proportional to body fat content. This is due to the relatively low water content of adipose tissue.

On the basis of these data, it has been estimated that the "reference" or average male contains 14 per cent fat and has a lean body mass which is composed of 71 per cent water<sup>16</sup> and that the average or "reference" female has a fat content which constitutes 28 per cent of total body weight and possesses a lean body mass in which the proportional amount of water is 72.6 per cent.<sup>12</sup> This suggests that the female is fatter and wetter than the male.

Little information is available concerning the gross body composition of pregnant women.

The present study, pertaining to the gross body composition of the pregnant individual, was initiated for the purpose of more accurately evaluating the pattern of change in total body water and exchangeable sodium which occurs during pregnancy.

### Material

Gross body composition, sodium<sup>22</sup> space, and total exchangeable sodium were determined in 16 normal pregnant patients, in 10 individuals in whom the clinical diagnosis of hypertensive toxemia had been made, in 8 individuals in whom an excess retention of water was the only clinical abnormality evident during pregnancy, and in 6 individuals with pre-eclampsia-eclampsia.

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Serial determinations were made during the last trimester of pregnancy and at the end of the first week of the puerperium in 7 normal pregnant patients, in 6 individuals who evidenced excessive weight gain, in 7 individuals with hypertensive toxemia, and in one individual with pre-eclampsia. Single determinations were made in 13, and two or more determinations were made in 27 of the 40 patients included in this study.

The patients with abnormal pregnancies as well as the normal individuals received no specific therapy in the antepartum period prior to the carrying out of these measurements. No individual received specific therapy in the postpartum period. Dieckmann's<sup>4</sup> criteria were employed in classifying the abnormal cases.

### Methods

The principles employed in this study have been derived from the fundamental work of Behnke,<sup>1</sup> Pace and Rathbun,<sup>21</sup> and Keys and Brozek.<sup>16</sup> The formulas pertaining to gross body composition are those of Siri.<sup>24</sup>

For the purpose of this study the products of conception were regarded as an integral part of the maternal organism. This organism was viewed as a four-compartment system composed of pure water, pure fat, minerals, and protein, in which the sum of the proportions of the four components was equal to unity when expressed in terms of weight or volume (Equations 1 and 2), with a proportional relationship existing between weight and volume, as expressed in Equation 3.

$$\text{Equation 1} \quad f + w + m + p = 1 \quad \text{unit weight}$$

$$\text{Equation 2} \quad F + W + M + P = 1 \quad \text{unit volume}$$

$$\text{Equation 3} \quad \frac{f}{df} + \frac{w}{dw} + \frac{m}{dm} + \frac{p}{dp} = \frac{1}{d} \quad \text{weight} = \text{density times volume}$$

When  $f, F$  = storage fat,  $w, W$  = pure water,  $m, M$  = minerals,  $p, P$  = protein, and  $df, dw, dm, dp$  = densities of fat, water, minerals, and protein, respectively.

Although "f" in Equation 3 consists of all substances with the density of the triglycerides which composed storage fat, it was assumed that "f" represented only storage fat.  $m + p$  constitute the sum of all components of the body which are not pure water and which are not triglycerides.

The following values were used for the densities of these components:

$$\begin{aligned} dw &= 0.993 \text{ Gm./cm.}^3 \text{ at } 37^\circ \text{ C.} \\ df &= 0.900 \text{ Gm./cm.}^3 \text{ at } 37^\circ \text{ C.}^{16} \\ dp &= 1.340 \text{ Gm./cm.}^3 \text{ at } 37^\circ \text{ C.}^{11} \\ dm &= 3.000 \text{ Gm./cm.}^3 \text{ at } 37^\circ \text{ C.}^2 \end{aligned}$$

Employing these values, Siri<sup>24</sup> has developed a formula for determining the proportion of fat in the living individual in which density and water occupy the roles of independent variables and in which the only assumption is that the ratio of mineral to protein is constant ( $m/p = k = 0.35$ ). His mathematical analyses have indicated that the biologic variations in this empirical relationship of minerals to proteins have relatively little effect on the reliability of this fat-estimating equation. This equation in its final form is:

$$f = \frac{2.118}{d} - 780w - 1.354$$

$$f = \text{proportion of fat per unit weight}$$

$$d = \text{total body density}$$

$$w = \text{proportion of total body water per unit weight}$$

This formula does not require a reference body nor an explicit description of the composition of adipose tissue.

TABLE I. SUMMARY OF THE DATA ON WHICH THE DETERMINATION OF THE GROSS BODY COMPOSITION OF THE NORMAL AND ABNORMAL PATIENTS INCLUDED IN THIS STUDY WAS BASED

PATIENT	WEEKS OF GESTA- TION	DAYS POST PARTUM	AGE	GRAVID- ITY	PARITY	WEIGHT (KG.)	DEN- SITY	FAT		D <sub>2</sub> O		Na <sup>22</sup> L.	Na <sup>22</sup> SPACE % FFBWT.	TES (MEQ./ KG. FFBWT.)	FAT FREE SOLIDS	
								%	KG.	L.	% FFBWT.				KG.	% FFBWT.
Normal Pregnancy.—																
F. V.	15		21	i	0	55.1	1.043	25.4	14.0	29.83	72.5	14.54	35.3	46.6	11.27	27.4
B. T.	15		19	iii	i	58.25	1.037	21.5	12.52	35.37	77.3	17.58	38.4	51.5	10.36	22.6
K. F.	16		21	i	0	69.8	1.037	26.5	18.5	38.15	74.3	18.48	36.0	48.6	13.15	25.6
L. H.	16		20	ii	i	44.76	1.050	18.8	8.41	27.3	75.1	14.21	39.0	51.6	9.05	24.8
Average								23.05	13.35	32.66	74.8	16.20	37.17	49.57	10.96	25.1
M. F.	20		18	i	0	57.0	1.051	14.7	8.38	37.6	77.3	19.24	39.5	53.4	11.02	22.6
K. D.	20		19	i	0	49.95	1.039	20.7	10.3	31.5	77.4	16.57	41.7	56.0	8.94	22.5
P. S.	20		24	i	0	54.35	1.051	19.1	10.38	32.93	74.8	15.75	35.8	49.0	11.04	25.1
A. C.	20		18	i	0	50.67	1.038	20.4	10.34	28.41	70.4	15.08	37.3	50.4	11.92	29.5
R. S.	20		20	ii	0	65.16	1.045	21.2	13.81	38.5	74.9	22.56	43.9	58.9	12.85	25.0
J. J.	21		18	i	0	73.05	1.017	30.5	22.3	39.94	78.6	13.75	27.0	36.2	10.81	21.3
Average								21.10	12.58	34.81	75.57	17.15	37.53	50.65	11.10	24.33
P. M.	28		20	i	0	60.55	1.037	24.8	15.01	34.27	74.5	17.4	38.2	52.4	11.27	24.7
J. Mc.	28		19	i	0	65.90	1.040	22.2	14.63	38.92	75.9	22.14	43.1	59.6	12.35	24.0
F. V.	30		21	i	0	60.50	1.036	23.1	15.1	35.67	78.5	15.22	33.5	46.2	9.73	21.4
K. F.	30		21	i	0	77.6	1.028	29.1	22.43	41.3	75.5	20.22	36.6	51.0	13.87	25.1
A. C.	30		18	i	0	55.31	1.026	24.5	13.55	33.02	79.0	16.35	39.1	55.2	8.74	20.9
M. F.	31		18	i	0	63.17	1.045	15.1	9.54	42.3	78.8	19.26	35.9	50.2	11.33	21.1
J. J.	32		18	i	0	79.88	1.017	35.0	27.95	38.67	74.4	22.12	42.5	52.1	13.26	25.5
M. B.	32		20	iii	ii	62.55	1.048	16.9	10.57	39.88	76.7	21.10	40.5	54.8	12.10	23.2
C. N.	32		35	ii	0	69.43	1.033	23.9	16.6	40.69	77.0	17.92	33.9	44.8	12.14	22.9
Average								23.84	16.15	38.30	76.70	19.08	38.14	51.81	11.64	23.2
P. M.	37		20	i	0	64.4	1.033	26.1	16.81	35.99	75.6	19.5	40.9	56.1	11.60	24.3
K. F.	37		21	i	0	81.67	1.022	28.7	23.44	45.23	77.6	24.4	41.9	55.3	11.00	22.3
F. V.	38		21	i	0	63.35	1.024	23.8	15.1	38.7	80.2	18.96	39.2	53.0	9.55	19.7
P. C.	38		19	i	0	57.9	1.046	10.8	6.25	41.77	80.8	19.94	38.6	50.2	9.88	19.1
M. B.	39		20	iii	ii	63.45	1.049	10.4	6.60	35.7	80.3	19.92	37.1	50.1	11.16	19.6
Average								19.96	13.64	39.47	78.90	20.54	39.54	52.94	10.64	21.0

Post partum:															
C. N.	8	35	ii	i	62.26	1.032	27.4	17.06	33.84	74.8	18.43	40.7	55.8	11.36	25.1
B. H.	10	24			65.4	1.002	42.0	27.5	28.46	75.0	14.4	37.9	52.2	9.44	24.9
P. M.	7	20	i	i	59.45	1.030	28.5	16.94	31.85	74.9	15.79	43.5	50.1	10.66	25.0
K. F.	7	21	i	i	72.71	1.016	30.4	22.1	39.54	78.1	19.13	37.7	51.0	11.07	21.8
F. V.	8	21	i	i	55.83	1.028	29.5	16.1	29.45	74.9	14.94	37.6	51.4	10.28	25.8
P. C.	7	19	i	i	55.86	1.039	28.5	17.89	27.55	76.5	17.8	49.4	69.8	8.42	23.4
M. B.	8	20	iii	iii	54.21	1.053	14.4	7.81	35.70	76.9	19.92	42.9	60.5	10.70	23.0
Average							28.67	17.91	32.34	75.87	17.20	41.39	55.83	10.23	24.14
Excessive Weight Gain.—															
B. S.	37	20	ii	i	90.45	1.005	34.9	31.57	46.90	79.6	21.97	37.3	51.1	11.98	20.3
A. R.	37	16	i	0	73.17	1.016	27.4	20.05	42.78	80.5	21.56	40.5	54.5	10.34	19.4
H. C.	37	24			96.00	1.010	33.9	32.05	49.81	77.1	23.22	36.3	48.3	14.14	22.9
M. R.	37	19	i	0	72.4	1.056	10.5	7.6	50.73	78.2	25.21	38.9	51.2	14.07	21.7
C. S.	38	22	iii	i	80.5	1.012	24.5	19.76	50.92	83.7	25.93	42.6	56.3	9.82	16.1
Average							26.24	22.20	48.22	79.82	23.57	39.12	52.28	12.07	20.1
Post partum:															
G. R.	7	17	i	i	45.05	1.030	27.4	12.34	33.84	76.2	14.27	43.6	57.6	7.77	23.7
B. S.	7	20	ii	ii	82.57	1.001	41.2	34.02	36.93	76.0	20.01	41.2	56.9	11.62	23.9
A. R.	7	16	i	i	66.70	1.010	34.1	22.74	34.02	77.3	17.38	39.5	53.0	9.94	22.6
H. C.	7	24			80.3	1.004	39.5	31.72	37.14	76.4	19.82	40.7	55.1	11.44	23.5
M. R.	7	19	i	i	64.85	1.032	21.3	13.81	40.36	79.0	21.22	41.5	55.7	10.68	20.9
C. S.	5	22	iii	ii	68.79	0.998	30.0	20.64	41.31	85.7	19.60	40.7	57.4	6.84	14.2
H. A.	7	19	i	i	64.95	1.017	34.0	22.08	32.31	75.3	17.97	41.9	59.1	10.56	24.6
Average							32.5	22.47	36.55	77.99	18.61	41.3	56.4	9.83	21.91
Hypertensive Toxemia.—															
H. B.	28	30	ii	i	80.15	1.036	28.1	22.52	42.05	72.9	19.68	34.1	46.1	15.58	27.0
E. V.	30	29	i	0	64.9	1.013	30.3	19.66	36.06	79.7	19.17	42.3	55.9	9.18	20.2
J. P.	32	29	ii	i	65.7	1.038	23.7	15.57	37.9	75.6	25.64	51.1	56.0	12.23	24.3
F. B.	33	16	ii	i	57.94	1.045	14.1	8.17	39.46	79.2	20.49	41.1	55.7	10.31	20.7
Average							24.05	16.48	38.86	76.85	21.24	42.15	53.43	11.83	23.05
E. L.	38	25	ii	i	79.62	1.017	33.6	26.75	40.1	75.8	21.35	40.3	54.1	12.77	24.1
E. W.	39	34	v	iv	88.71	1.041	17.5	15.52	57.55	78.6	25.46	34.7	48.7	15.64	21.3
B. C.	39	20	ii	i	75.34	1.033	30.9	23.28	37.42	71.8	24.97	47.9	63.3	14.64	28.1
Average							27.33	21.85	45.02	75.4	23.92	40.97	55.37	14.35	24.5

TABLE I—CONT'D

PATIENT	WEEKS OF GESTA- TION	DAYS POST- PARTUM	AGE	GRAVID- ITY	PARITY	WEIGHT (KG.)	DEN- SITY	FAT		D <sub>2</sub> O		Na <sup>22</sup> SPACE % FFBWT.	TES (MEQ./ KG. FFBWT.)	FAT OR EE SOLIDS	
								%	KG.	L.	%			KG.	%
<i>Post partum:</i>															
J. P.	9		29	ii	ii	57.3	1.063	19.9	11.4	32.27	70.3	18.83	56.6	13.63	29.1
H. E.	10		27	ii	ii	133.1	0.997	45.7	60.83	53.54	73.9	26.52	50.6	18.83	26.0
H. B.	5		30	ii	ii	72.43	1.006	37.5	27.16	34.98	77.2	17.26	51.1	10.29	22.7
E. V.	8		29	i	i	58.27	1.036	24.3	14.16	33.4	75.7	16.31	48.8	10.71	24.2
F. B.	10		16	ii	ii	50.50	1.041	20.5	10.35	30.8	76.7	16.92	48.6	9.35	23.2
E. L.	8		25	ii	ii	70.82	1.010	39.6	28.04	31.66	74.0	17.14	53.6	11.12	25.9
E. W.	8		34	v	v	78.62	1.036	27.3	21.46	42.11	73.6	21.84	47.4	15.05	26.3
B. C.	5		20	ii	ii	63.02	1.023	27.9	17.58	35.34	77.7	18.43	54.8	10.10	22.2
Average								30.33	23.87	36.76	74.88	19.15	51.43	12.38	24.95
<i>Pre-eclampsia-Eclampsia.—</i>															
M. H.	39		26	i	0	87.85	1.041	14.3	12.56	60.58	80.4	35.58	62.4	14.71	19.5
D. A.	38		16	i	0	82.59	1.015	32.5	26.84	43.18	77.4	26.52	63.7	12.57	22.5
M. T.	39		26	i	0	68.69	1.036	7.1	4.88	54.55	85.4	30.66	65.0	9.26	14.5
B. H.	39		23	iv	iii	84.21	1.021	22.7	19.17	53.5	82.2	33.24	70.2	11.54	17.7
Average								19.15	15.86	52.95	81.35	31.5	65.33	12.02	18.55
<i>Post partum:</i>															
M. Ha.	10		26	i	i	71.83	1.041	25.7	18.46	38.98	73.0	27.91	69.0	14.39	26.9
R. S.	10		15	i	i	61.92	1.026	19.8	12.26	40.69	81.9	23.36	63.5	8.97	18.0
M. He.	14		35			76.65	0.992	35.2	26.98	42.2	84.9	25.6	72.7	7.47	15.0
Average								26.9	19.23	40.62	79.93	25.62	68.4	10.28	19.97
<i>Normal Adults.—</i>															
Man	28					71.74	1.058	22.0	15.78	39.33	71.2	19.87	50.8	16.63	28.7
Nonpregnant woman	30					55.25	1.038	29.4	16.24	27.8	70.2	14.45	49.0	11.21	29.7



The percentage of fat was determined by this equation and the values for fat-free body weight and fat-free solids were obtained as follows:

Equation 4      weight of fat = body weight times % fat

Equation 5      fat-free body weight = total body weight minus  
weight of fat

Equation 6      weight of fat-free solids = fat-free body weight  
minus weight of total body water

Total body water was determined by means of  $D_2O$ , by the falling drop method of Schloerb and associates.<sup>22</sup>

Sodium<sup>22</sup> space and total exchangeable sodium were determined by the method of Dieckmann and Pottinger.<sup>7</sup>

Body density was determined by the method of underwater weighing, which has been described by Behnke and associates.<sup>1</sup>

The difference between body weight in air and the weight of the body completely submerged in water at maximal expiration when corrected for the thermal coefficient of expansion of water at the prevailing water temperature and when corrected for residual air was employed in calculating body density. The helium dilution technique of Wilmont and Behnke<sup>26</sup> was employed for the determination of residual air.

The following equation was employed in calculating total body density:

$$\text{Equation 7} \quad D_b = \frac{Ma}{\frac{Ma \times M'w - V_r}{D_w}}$$

$D_b$  = body density

$Ma$  = weight in air

$M'w$  = apparent weight in water

$V_r$  = volume of residual air

$D_w$  = density of water

### Results

Data pertaining to the entire group of patients are listed in Table I. A summary of the data relative to the average composition of the fat-free body is contained in Table II.

*Normal Pregnant Patients.*—Tables III and IV illustrate the alterations in gross body composition which occur during normal pregnancy.

The weight of K. F. increased from 69.8 kilograms at 16 weeks' gestation to 81.64 kilograms at 37 weeks' gestation (Table III). A decrease in density from 1.037 to 1.022 occurred during this period. The proportion of pure fat increased from 26.5 to 28.7 per cent of body weight. The absolute increase in this component was 5 kilograms. There was a 7 kilogram increase in fat-free body weight, which was accompanied by a 7 kilogram increase in total body water. The absolute amount of fat-free solids decreased during the last trimester of pregnancy.

A comparison of term and postpartum values disclosed that this individual had lost 8.6 kilograms in weight by the seventh postpartum day. This was the result of a loss of 5.69 kilograms of water, 1.93 grams of fat-free solids, and 1.3 kilograms of fat. The proportion of pure fat had increased to 34.4 per cent of total body weight.

A net retention of 1.39 kilogram of water, a net gain of 3.6 kilograms of fat, and a net loss of 2 kilograms of solids, which were evident in the postpartum period, as compared with the values which obtained at 14 weeks' gestation were reflected in relative densities of 1.037 and 1.016.

F. V. gained 8.5 kilograms in weight during a 23 week period of prenatal observation (Table V). During this period, which extended from the fifteenth

to the thirty-eighth week of gestation, total body density decreased from 1.043 to 1.024. Although the proportion of storage fat decreased from 25 to 24 per cent of body weight during this period, there was an absolute increase of 1 kilogram in this component. There was a 7.4 kilogram increase in fat-free body weight which was accompanied by an 8.9 kilogram increase in total body water and a 1.6 kilogram decrease in the amount of fat-free solids. The fat-free body at term contained 9.55 kilograms of solids and 38.7 kilograms of water.

At 8 days post partum, this individual had lost 7.7 kilograms of weight and had a density of 1.028. The proportion of pure fat had increased to 30 per cent of body weight.

TABLE II. AVERAGE COMPOSITION OF THE FAT-FREE BODY

	% FAT-FREE BODY WEIGHT			EXCHANGEABLE SODIUM (mEq./kg.)
	TOTAL BODY WATER (D <sub>2</sub> O)	Na <sup>22</sup> SPACE (3 HOUR)	FAT-FREE SOLIDS	
<i>Normal Pregnancy.—</i>				
15-16 weeks	74.80	37.17	25.1	49.57
20-21	75.57	37.53	24.33	50.65
28-32	76.70	38.14	23.2	51.81
37-39	78.90	39.54	21.0	52.94
Post partum	75.87	41.39	24.14	55.83
<i>Hypertensive Toxemia.—</i>				
28-33 weeks	76.85	42.15	23.05	53.43
38-39	75.4	40.97	24.5	55.37
Post partum	75.47	38.78	24.38	51.07
<i>Excessive Weight Gain.—</i>				
37-38 weeks	79.82	39.12	20.1	52.28
Post partum	77.90	41.30	21.91	56.40
<i>Pre-eclampsia-Eclampsia.—</i>				
38-39 weeks	81.35	47.8	18.55	65.33
Post partum	79.93	50.23	19.97	68.4
<i>Normal Adults.—</i>				
Nonpregnant women	70.2	35.5	29.7	49.0
Man	71.2	37.0	28.7	50.8

On the basis of fat-free body weight, the normal pregnant patients evidenced a progressive increase in water content from an average of 75 per cent at the beginning of the second trimester of pregnancy to 79 per cent at term (Table II, Fig. 1). The average sodium space increased from 37 to 40 per cent. The average amount of exchangeable sodium contained in 1 kilogram of the fat-free body increased from 49.6 to 52.9 mEq. at term. The average percentage of fat-free solids decreased from 25 to 24. At the end of the first week post partum, the average relative proportions of water and solids contained in the fat-free body were 76 and 24 per cent, respectively. The sodium space was 41 per cent of fat-free body weight, and 1 kilogram of the fat-free body contained 56 mEq. of exchangeable sodium.

*Hypertensive Disease.*—Average term values for water, solids, sodium<sup>22</sup> space, and exchangeable sodium in the fat-free body of individuals with hypertensive disease were 75 per cent, 25 per cent, 41 per cent, and 55 mEq. per kilogram, respectively (Table II, Fig. 2). At the end of the first week post partum, values for water, solids, sodium<sup>22</sup> space, and exchangeable sodium were 76 per cent, 24 per cent, 39 per cent, and 51 mEq. per kilogram, respectively.

TABLE III. REPRESENTATIVE VALUES FOR BODY COMPOSITION AS DETERMINED IN THE LIVING PREGNANT INDIVIDUAL

<i>K. F., age 20 years, gravida i, para 0, height 175.5 cm., surface area 1.85 sq. M.</i>				
Weeks' gestation	16	30	37	7 days post partum
Weight (kg.)	69.8	77.6	81.67	72.71
Density	1.037	1.028	1.022	1.016
Total body water (D <sub>2</sub> O) (L.)	38.15	41.30	45.23	39.54
Sodium <sup>22</sup> space (3 hour) (L.)	18.48	20.22	24.4	19.13
Total exchangeable sodium (mEq.)	2,495	2,790	3,221	2,583
% total body weight:				
Total body water (D <sub>2</sub> O)	54.6	52.5	55.4	54.3
Sodium <sup>22</sup> space (3 hour)	26.4	26.0	29.8	26.3
Fat	26.5	29.1	28.7	30.4
Solids	18.8	17.8	15.9	15.2
% fat-free body weight:				
Total body water (D <sub>2</sub> O)	74.3	74.8	77.6	78.1
Sodium <sup>22</sup> space (3 hour)	36.0	36.6	41.9	37.7

TABLE IV. REPRESENTATIVE VALUES FOR BODY COMPOSITION AS DETERMINED IN THE LIVING PREGNANT INDIVIDUAL

<i>F. V., age 21 years, gravida i, para 0, height 166 cm., surface area 1.61 sq. M.</i>				
Weeks' gestation	15	30	38	8 days post partum
Weight (kg.)	55.1	60.5	63.55	55.83
Density	1.043	1.036	1.024	1.028
Fat (kg.)	14.0	15.1	15.1	16.1
Solids (kg.)	11.27	9.73	9.55	10.28
Total body water (D <sub>2</sub> O) (L.)	29.83	35.67	38.7	29.45
Sodium <sup>22</sup> space (3 hour) (L.)	14.54	15.22	18.96	14.94
Total exchangeable sodium (mEq.)	1,919	2,100	2,560	2,017
% total body weight:				
Total body water (D <sub>2</sub> O)	54.1	58.9	61.0	52.7
Sodium <sup>22</sup> space (3 hour)	26.3	25.1	29.9	26.7
Fat	25.4	23.1	23.8	29.5
Solids	20.4	16.0	15.0	18.4
% fat-free body weight:				
Total body water (D <sub>2</sub> O)	72.5	78.5	80.2	74.2
Sodium <sup>22</sup> space (3 hour)	35.3	33.5	39.2	37.6
Solids	27.4	21.4	19.7	25.8
Exchangeable sodium (mEq./kg. body weight)	34.8	34.7	40.4	36.1
Exchangeable sodium (mEq./kg. fat-free body weight)	46.6	46.2	53.0	51.4

**Excessive Weight Gain.**—Average term values for the composition of the fat-free body of individuals who evidenced an excessive weight gain during pregnancy and who were regarded as having stored excessive amounts of water, but who were otherwise normal, were as follows: water, 80 per cent; fat-free solids, 20 per cent; sodium<sup>22</sup> space, 39 per cent; and exchangeable sodium, 52 mEq. per kilogram (Table II, Fig. 2). The average composition of the fat-free body in these individuals at the end of the first postpartum week was as follows: water, 78 per cent; solids, 22 per cent; sodium<sup>22</sup> space, 41 per cent; and exchangeable sodium, 56 mEq. per kilogram.

**Pre-eclampsia-Eclampsia.**—Average term values for water, sodium<sup>22</sup> space, exchangeable sodium, and solids contained in the fat-free bodies of the individuals with pre-eclampsia-eclampsia were 81.4 per cent, 47.8 per cent, 65.3 mEq. per kilogram, and 18.6 per cent, respectively (Table II, Fig. 2). During the first week post partum, the average composition of the fat-free body of these individuals was as follows: water, 79.9 per cent; sodium<sup>22</sup> space, 50.2 per cent; exchangeable sodium, 68.4 mEq. per kilogram; fat-free solids, 20 per cent.

TABLE V. RELATIONSHIP BETWEEN FAT AND THE PROPORTIONAL AMOUNT OF WATER CONTAINED IN THE FAT-FREE BODIES OF NORMAL PREGNANT PATIENTS AT THE END OF THE FIRST POSTPARTUM WEEK

PATIENT	PARITY	DAYS POST PARTUM	WEIGHT (KG.)	SURFACE AREA (SQ. M.)	DENSITY	FAT (KG.)	FAT-FREE SOLIDS (KG.)	FAT-FREE BODY		
								TOTAL BODY WATER (D <sub>2</sub> O) (%)	Na <sup>22</sup> SPACE (3 HOUR) (%)	EXCHANGEABLE SODIUM (MEQ./KG.)
B. H.	i	10	74.7	1.71	1.002	27.5	9.4	75.0	37.9	52.2
K. F.	i	7	72.7	1.85	1.016	22.1	11.1	78.1	37.7	51.0
P. C.	i	7	53.9	1.63	1.039	17.9	8.42	76.5	49.4	69.8
C. N.	i	8	62.3	1.84	1.032	17.1	11.4	74.8	40.7	55.8
P. M.	i	7	59.5	1.66	1.030	16.9	10.7	74.9	43.5	50.1
F. V.	i	8	55.8	1.61	1.028	16.1	10.3	74.9	26.7	51.4
M. B.	ii	8	54.2	1.66	1.053	7.8	10.7	76.9	42.9	60.5



**Normal Nonpregnant Individuals.**—Composition of the fat-free body of one normal 30-year-old nonpregnant woman was as follows: water, 70.2 per cent; sodium<sup>22</sup> space, 35.5 per cent; exchangeable sodium, 49.0 mEq. per kilogram; fat-free solids, 29.7 per cent (Table II). Values for one 28-year-old normal man were: water, 71.2 per cent; sodium<sup>22</sup> space, 37 per cent; total exchangeable sodium, 50.8 mEq. per kilogram; fat-free solids, 28.7 per cent (Table II).

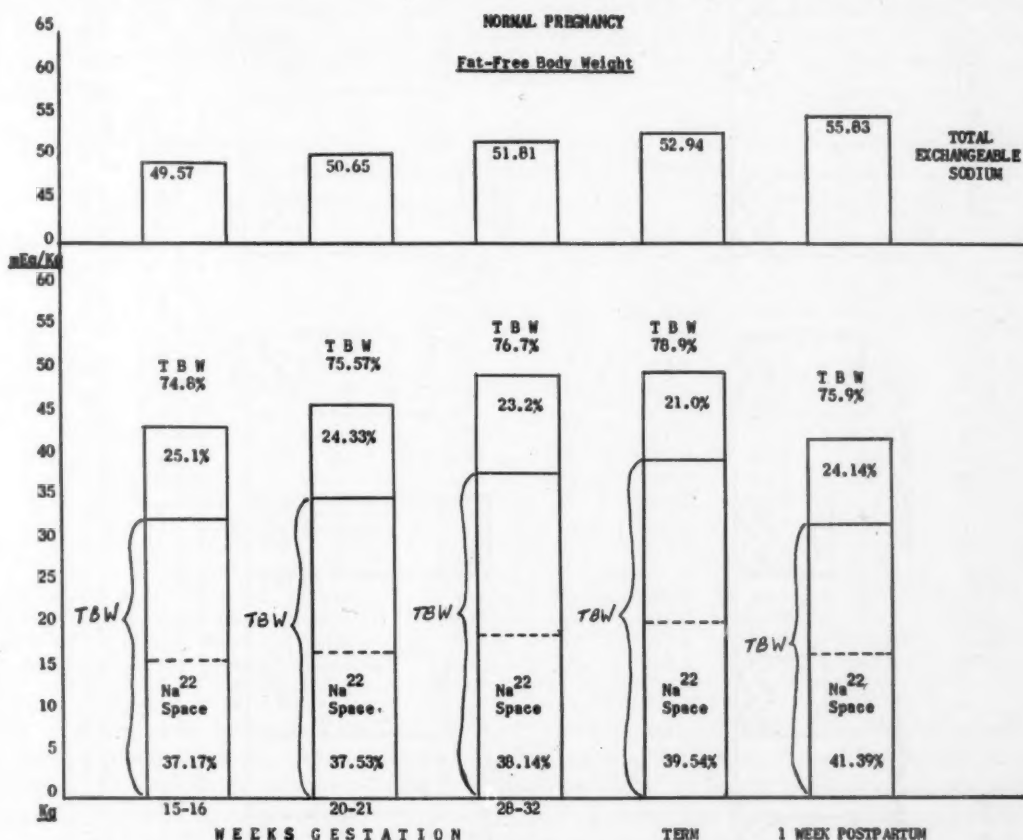


Fig. 1.—Average fat-free body composition of normal gravid individuals. This illustrates the relative magnitude of the progressive prenatal retention of water and exchangeable sodium which occurred in this group of individuals.

### Comment

The facts that water and sodium retention are concomitants of normal pregnancy and are marked in pre-eclampsia-eclampsia, and that these changes are associated with increases in sodium<sup>22</sup> space and extracellular fluid are well documented in the literature.<sup>3, 6, 7, 10, 13-15, 17</sup> A better appreciation of this pattern of change is achieved when these components are evaluated from the standpoint of gross body composition. In addition, measurements related to the fat-free body constitute a more accurate basis for making group comparisons than relative values based on total body weight. The error inherent in basing comparative values on total body weight is illustrated by the fact that in this study the quantity of body fat varied from 8 to 60 per cent of total body weight and net increases at term of 4 kilograms of pure fat were not uncommon in individual patients.

Although the range of variability was limited when group comparisons were made, the proportions of water, sodium<sup>22</sup> space, and exchangeable sodium

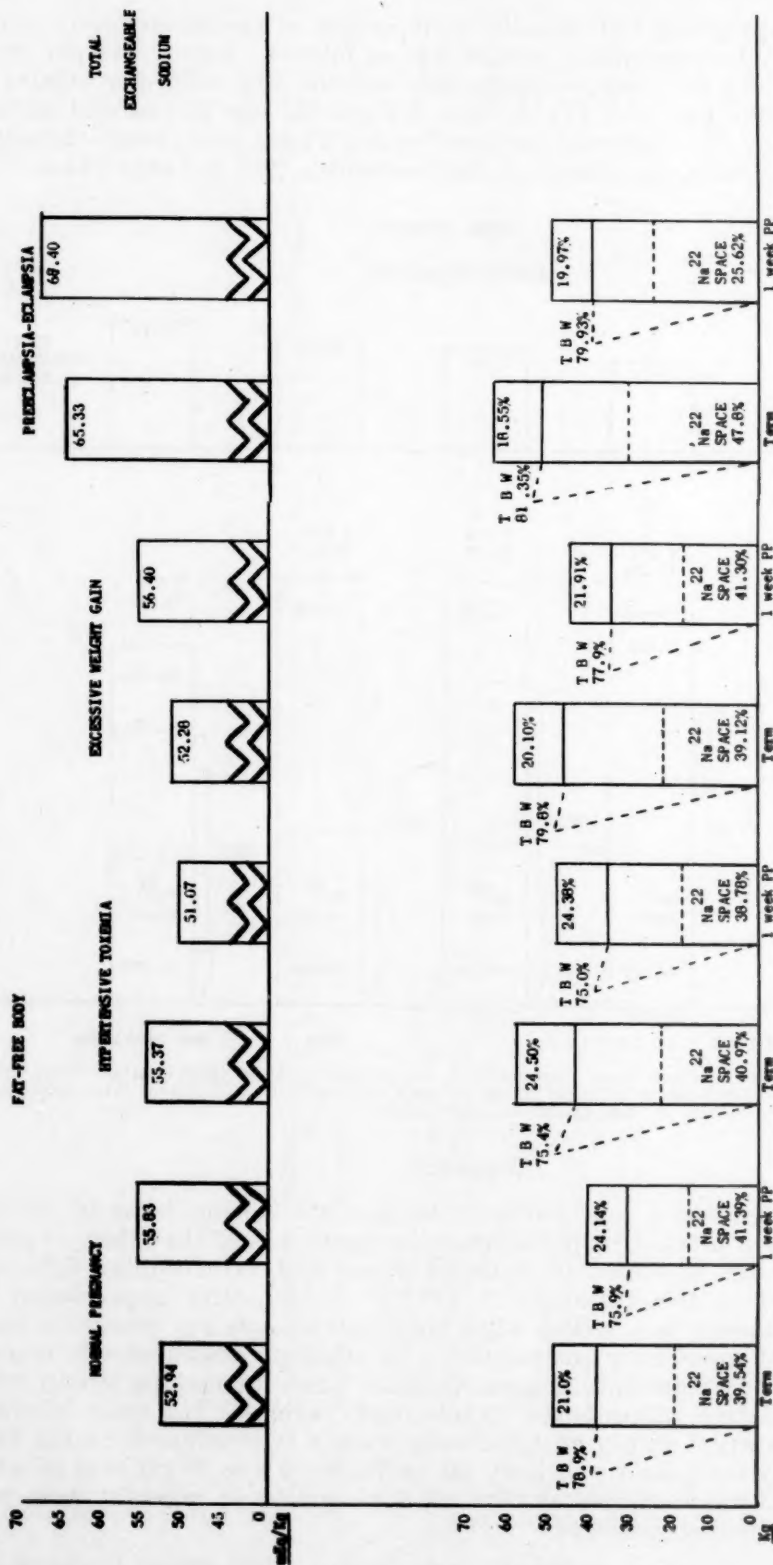


Fig. 2.—Normal and abnormal pregnant patients. Average fat-free body composition at term and at one week post partum. Because of lesser amounts of body water and solids, the average fat-free body weight of the normal pregnant patients was less than that of the other groups. The proportion of water present in the fat-free bodies of the individuals with hypertensive toxemia was lower than that which obtained in the other patients. This relative change in body composition, which characterized the individuals with hypertensive disease, was the result of an increase in the absolute amount of fat-free solids. The greater average fat-free body weight which occurred in the pre-eclampsia-eclampsia group was the result of an increase in the absolute amount of body water. The individuals with pre-eclampsia-eclampsia were unique in that they evidenced marked proportional increases in the amount of exchangeable sodium both at term and at the end of the first postpartum week.

contained in the fat-free body at a given period of gestation were not constant. It is our belief that variability in individual responses to the stimuli for water and sodium retention, which are inherent in the pregnant state, was the critical factor mediating these differences and that variability in the mass of the products of conception and in the quantity of adipose tissue were of secondary importance. The fact that the amount of extracellular fluid associated with adipose tissue was not a critical influential factor in these proportional differences in total body water is illustrated in Table V, which relates fat to total body water in normal pregnant patients at the end of the first week post partum.

TABLE VI. SODIUM<sup>22</sup> SPACE AND EXCHANGEABLE SODIUM. TERM AND POSTPARTUM VALUES BASED ON FAT-FREE BODY WEIGHT

		WEEKS ANTE PARTUM	DAYS POST PARTUM	Na <sup>22</sup> SPACE (%)		EXCHANGEABLE SODIUM (mEq./kg.)	
				ANTE PARTUM	POST PARTUM	ANTE PARTUM	POST PARTUM
K. F.	Normal	37	7	41.9	37.7	55.3	51.0
F. V.	Normal	38	8	29.9	26.7	53.0	51.4
B. H.	Normal	36	10	37.9	37.9	52.2	50.4
P. M.	Normal	37	7	40.9	43.5	56.1	50.1
M. B.	Normal	39	8	37.1	42.9	50.1	60.5
P. C.	Normal	38	7	38.6	49.4	50.2	69.8
C. N.	Normal	36	8	37.8	40.7	51.0	55.8
A. R.	Excessive weight gain	36	7	40.5	39.5	54.5	53.0
C. S.	Excessive weight gain	38	5	42.6	40.7	56.3	57.3
B. S.	Excessive weight gain	36	7	37.3	41.2	51.1	56.9
M. R.	Excessive weight gain	37	7	38.9	41.3	51.2	55.7
E. L.	Hypertensive disease	38	8	40.3	40.0	54.1	53.6
E.W.	Hypertensive disease	39	8	34.7	38.2	48.7	47.4
B. C.	Hypertensive disease	39	5	47.9	40.5	63.3	54.8
M. Ha.	Pre-eclampsia-eclampsia	39	10	44.6	52.2	62.4	69.0

Care was exercised to insure that these measurements were made under constant conditions. Hence, it is felt that errors resulting from the techniques employed were consistent in each individual and at each period of gestation and that the values which were obtained present an accurate picture of the relative changes which occurred in the gross body composition of these individuals.

There were significant changes in the fat-free bodies of the four groups of individuals. The absolute amount of total body water was the major factor mediating these variations. Since exchangeable sodium was calculated from the sodium<sup>22</sup> space, the proportional amount of sodium contained in the fat-free body was related to this space.

Because of lesser absolute amounts of body water and solids, the average fat-free body weight of the normal pregnant patients was less than that of the other groups.

There was a 2 per cent maximum average term difference in the proportion of water contained in the fat-free bodies of normal pregnant patients, individuals who evidenced excessive weight gain, and individuals with pre-eclampsia-eclampsia. The proportion of water present in the fat-free bodies of the individuals with hypertensive toxemia was lower than that which obtained in the other groups. This relative change in body composition which characterized the individuals with hypertensive disease was the result of an increase in the absolute amount of fat-free solids.

TABLE VII. TOTAL BODY DIRECT CHEMICAL ANALYSIS

SEX	AGE (YEARS)	WEIGHT (KG.)	HEIGHT (CM.)	% BODY WEIGHT			% FAT-FREE WEIGHT			INVESTIGATOR	REMARKS
				FAT	WATER	SOLIDS	WATER	SOLIDS			
Female	42	45.1	169	23.6	56.0	22.0	73.2	28.7		Widdowson <sup>25</sup>	Suicide by drowning
Male	25	71.8	179	14.9	61.8	24.1	72.6	26.3		Widdowson <sup>25</sup>	Died of uremia
Male	35	70.6	183	12.5	67.9	23.2	77.6	22.0		Mitchell <sup>19</sup>	Cardiac failure
Male	46	53.8	168.5	19.4	55.1	24.0	68.4	29.8		Forbes <sup>9</sup>	Died one week after a cerebral injury
Male	48	63.8		1.1	81.5	17.7	82.4	17.9		Widdowson <sup>25</sup>	Wasted and edematous



Since the average amount of solids contained at term in the fat-free bodies of individuals with excessive weight gain and with pre-eclampsia-eclampsia were the same, the greater average fat-free body weight evidenced by the pre-eclampsia-eclampsia group was the result of an increase in the absolute amount of body water.

There was a 2 per cent maximum average term difference in the proportion of sodium<sup>22</sup> space contained in the fat-free bodies of normal pregnant patients, individuals with hypertensive disease, and individuals with excessive weight gain. The individuals with pre-eclampsia-eclampsia evidenced marked proportional increases in the sodium<sup>22</sup> space and in the amount of exchangeable sodium, both at term and at the end of the first postpartum week. Since this combination of antepartum and postpartum changes was unique in this group of individuals, it is possible that these changes may constitute a physicochemical definition of pre-eclampsia-eclampsia.

A comparison of the average term and postpartum values for the composition of the fat-free body of normal pregnant patients, individuals with excessive weight gain, and patients with pre-eclampsia-eclampsia revealed that there was a decrease in the proportions of water and an increase in sodium<sup>22</sup> space and exchangeable sodium during the puerperium. These changes in the sodium<sup>22</sup> space and exchangeable sodium did not occur in individuals with hypertensive disease, and a review of the data discloses that they occurred in 45 per cent of the combined groups with normal pregnancy and excessive weight gain (Table VI). This phenomenon did not appear to be related to age, parity, or degree of obesity. The factors responsible for this relative increase in exchangeable sodium in the puerperium are unknown. It is possible that the extracellular fluid was hypotonic or that the sodium was held in an osmotically inactive form in the ground substance of the connective tissue, intracellularly or in bone, during the antepartum period. These changes are in accord with balance studies conducted during the puerperium on patients with pre-eclampsia-eclampsia in which it was found that these individuals consistently excreted greater proportional amounts of water than sodium<sup>6</sup>

The fact that two clinically normal individuals evidenced puerperal changes in their fat-free body composition which were of the same order as those exhibited by the individuals with pre-eclampsia-eclampsia is of interest. These findings suggest that these individuals retained abnormal amounts of sodium during pregnancy, and that their sodium metabolism was maintained within the normal limits for pregnancy by mechanisms which rendered the excess sodium physiologically inactive.

Contrary to the observations of Seitchik and Alper,<sup>23</sup> the individuals in this study did not evidence a consistent progressive loss of storage fat during pregnancy, in that 75 per cent of 12 patients gained from 1.2 to 5.6 kilograms of fat during periods of observation which varied from 7 to 23 weeks. These authors found that the pregnant patients whom they studied evidenced a gain in total body water which exceeded the increment in body weight. Although this phenomenon was evident in our patients, exceptions occurred. In the instances where this obtained there was a compensatory decrease in the absolute amount of fat-free solids. We have no explanation for this, other than that it may constitute a measure of the error inherent in the methods employed.

At term, the proportional relationships of the sodium<sup>22</sup> space and exchangeable sodium in the majority of individuals with hypertensive toxemia did not differ from those which obtained in the normal pregnant group. This

is in agreement with previous investigations in which it was found that the ability of the pregnant patient with hypertensive disease to handle a sodium load was within the limits of that for normal pregnancy.<sup>5</sup>

Direct total body chemical analyses are required for the validation of these and similar indirect determinations of gross body composition. Acceptable chemical analyses of adult cadavers are currently limited to the four male and the one nonpregnant female body which are listed in Table VII. Hence, values based on direct chemical determinations are not available for the pregnant individual.

Two of the four male cadavers presented clinical evidence of excessive hydration. When related to fat-free body weight the proportions of body water were 77.6 and 82.4 per cent, and the proportions of solids were 22 and 17.9 per cent in these individuals. There is a close correlation between this chemical evidence of excessive hydration and the values which were obtained in this study.

### Summary

Gross body composition, sodium<sup>22</sup> space, and exchangeable sodium were determined in normal and abnormal pregnant patients.

The pattern of alteration in gross body composition which characterized normal pregnant patients, individuals who evidenced excessive weight gain as the only clinical abnormality, individuals with hypertensive disease, and patients with pre-eclampsia-eclampsia are presented.

The individuals with pre-eclampsia-eclampsia were unique in that they evidenced marked antepartum and postpartum increases in the proportion of exchangeable sodium contained in their fat-free bodies. It was suggested that this combination of antepartum and postpartum changes may constitute a physicochemical definition of pre-eclampsia-eclampsia.

We wish to acknowledge our indebtedness to the late Dr. William J. Dieckmann, who was an active participant in this study.

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## ALTERATIONS IN BODY FLUID COMPARTMENTS AND EXCHANGEABLE SODIUM IN THE EARLY PUERPERIUM\*

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IT HAS been almost generally accepted, for decades, that normal pregnancy is associated with hydration of the maternal tissues and the retention of rather large amounts of water and sodium, which are lost in the early puerperium (for review of the literature, see Chesley<sup>1</sup>).

In the present paper a group of just-delivered, normal women will be compared to a matched group of nonpregnant women, with respect to volumes of distribution of T-1824 (plasma volume ?), sucrose (extracellular fluid volume ?), sodium<sup>24</sup> and the 24 hour exchangeable sodium. Eleven of the just-delivered women were kept on balance studies for a week after delivery and the measurements were then repeated. Attempted measurements of total body water with N-acetyl-4-amino-antipyrine (NAAP)<sup>2</sup> were not satisfactory.

### Material and Methods

The "normal puerperal" group consisted of 21 women selected on the basis of their having had normal antepartal courses, short and easy labors, average body build, and no evidence of dehydration. The measurements were started within 2 hours after delivery. The nonpregnant group consisted of 16 women from the gynecologic wards. They were selected on the basis of their minor pathoses and no evidence of dehydration. Other factors in the selection were body weight and body build, because an effort was made to match this group with the "normal puerperal" subjects. The nonpregnant women were older, on the average, but all were within the childbearing age. All women were fasting when the tests were begun.

One variable of possible importance was not controlled, and this was the diet prior to the measurements. The just-delivered women had been admitted in labor only a few hours before the tests, while the nonpregnant women had been in the hospital for several days and on the regular house diet containing 2,000 calories and about 90 mEq. of sodium. The balance studies, in the first 7 days of the puerperium, were initiated with no foreperiod on the diet.

The volume of sucrose distribution was measured by the calibrated infusion method of Deane, Schreiner, and Robertson<sup>3</sup>; as soon as the sucrose

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infusion was started, 50 ml. of NAAP in 2 per cent solution and 30  $\mu\text{c}$  of  $\text{Na}^{24}$  in saline were run into the infusion tubing from calibrated burettes. T-1824 was injected by syringe; the exact amount of dye given was ascertained by weighing the syringe and needle before and after the injection. The volume of sucrose distribution was calculated in 3 or 4 consecutive periods; the first calculation was made from samples taken about 90 minutes after the start of the infusion. Venous blood samples were taken, with no anticoagulant, both for the sucrose measurements and, subsequently, at hourly intervals up to 8 hours after the injection of the NAAP. Another blood sample was taken 24 hours after the injection of the  $\text{Na}^{24}$ . During the measurements of the sucrose space the urine outputs were obtained by an indwelling, multiple-eyed catheter, water rinses and air flushings being used in the usual way. Thereafter the completion of the 24 hour urine collection was made without a catheter.

In the balance studies, done in 11 puerperal women, each item of the diet was weighed and an exact duplicate saved for analysis. All food rejected by the patient was saved and analyzed separately. The duplicate of the diet was homogenized in a Waring blender with tap water to match the amount drunk by the patient; if more fluid was needed to make the slurry, the extra amount was made up of distilled water. The homogenate was weighed (usually 2,500 to 3,000 Gm.) and duplicate aliquots (3 to 5 Gm.) were accurately weighed for analysis. These were wet-ashed<sup>4</sup> and the digests then diluted to suitable volumes for flame photometric analysis. Rejected portions of the diet and the fecal outputs of the patients were treated in the same way. All urine was collected in 24 hour periods. Sodium and potassium analyses were done with a Perkin-Elmer 52C flame photometer, using an internal lithium standard. Blank analyses showed that the acid digestion mixture was free of sodium and potassium. The acidity of the final solutions did not affect the results, as shown by recovery experiments. None of the mothers nursed her infant. Lochia was not analyzed.

Sucrose was measured, in duplicate or quadruplicate, by the method of Roe, Epstein, and Goldstein<sup>5</sup>; serum proteins were precipitated by zinc hydroxide. NAAP was measured by the method of Brodie and associates.<sup>2</sup> Integral bias counts were made of the  $\text{Na}^{24}$  with a gamma spectrometer; the accumulation of 10,000 to 15,000 counts, in serum samples and standards, kept the standard deviation of the total counts below 1 per cent. In all of these analyses, duplicate samples of the solutions injected into the patients were suitably diluted and carried through with the serum and urine measurements. T-1824 was read in serum from blood taken 10 minutes after injection of the dye. All photometric readings were made with a Beckman DU spectrophotometer.

### Results

The chemical method used for NAAP gave excellent recoveries in sera containing known amounts of this substance. However, erratic results were obtained in the analyses of the patients' sera. The 6 points plotted for each case seldom fell on an exponential curve and there was usually so much doubt as to where the origin of the curve should be placed that the results were unreliable. This was true in the nonpregnant as well as in the just-delivered women.

*Comparison of Just-Delivered Women With Nonpregnant Women.*—The data for the nonpregnant women are summarized in Table I, and for the just-delivered women in Table II. Sucrose spaces are not shown for one of the former and 5 of the latter because equilibrium was not established in these

TABLE I. DATA FOR NONPREGNANT WOMEN

NO.	AGE	WEIGHT (Kg.)	SURFACE AREA M. <sup>2</sup>	VOLUMES OF DISTRIBUTION						EXCHANGEABLE SODIUM	
				SUCROSE		4 HOUR NA <sup>24</sup>		T-1824		mEq./Kg.	mEq./M. <sup>2</sup>
				ML./Kg.	L./M. <sup>2</sup>	ML./Kg.	L./M. <sup>2</sup>	ML./Kg.	L./M. <sup>2</sup>		
1	36	47.5	1.45	198	6.48	273	8.96	45.1	1.475	42.7	1,400
2	28	51.9	1.58	180	5.93	267	8.78	39.3	1.292	43.2	1,415
3	23	52.3	1.58	192	6.36	288	9.50			44.3	1,467
4	29	55.0	1.54	157	5.62	249	8.90	46.7	1.665	41.4	1,478
5	30	56.4	1.58	155	5.53	229	8.16				
6	24	60.7	1.64	217	8.02	240	8.90	37.5	1.387	35.4	1,312
7	23	60.9	1.68	201	7.29			49.5	1.795		
8	30	62.0	1.69	185	6.79	319	11.68	49.7	1.823	44.8	1,645
9	42	62.8	1.66	158	5.99			36.6	1.385		
10	32	63.6	1.70			254	9.50	39.6	1.482	39.7	1,483
11	30	69.2	1.81	149	5.72	236	9.02	36.9	1.412	36.9	1,412
12	39	72.4	1.71	192	8.16	281	11.90	42.4	1.798	39.9	1,690
13	37	75.1	1.79	140	5.87	222	9.33	34.6	1.452	34.5	1,448
14	37	75.2	1.83	154	6.32	236	9.67			36.6	1,504
15	27	77.8	1.92	137	5.55	261	10.58				
16	35	80.2	1.83	118	5.16	212	9.29	32.1	1.405	32.9	1,445
Median	30	62.4	1.69	158	5.99	252	9.31	39.5	1.462	39.7	1,458
Mean	31.4	64.0	1.69	169	6.32	254	9.59	40.8	1.530	39.4	1,475
Standard deviation	5.6	9.7	0.12	27	0.88	28	1.04	5.6	0.18	3.9	99

TABLE II. DATA FOR WOMEN JUST DELIVERED

NO.	AGE	WEIGHT (KG.)	SURFACE AREA M. <sup>2</sup>	VOLUMES OF DISTRIBUTION						EXCHANGEABLE SODIUM	
				SUCROSE		4 HOUR NA <sup>24</sup>				T-1824	
				ML./KG.	L./M. <sup>2</sup>	ML./KG.	L./M. <sup>2</sup>	ML./KG.	L./M. <sup>2</sup>	ML./KG.	M.EQ./KG.
1	24	48.5	1.49	146	5.23	264	8.60	40.6	1.322	39.9	1,298
2	22	51.1	1.43	187	6.54	280	10.00	49.3	1.762	38.9	1,388
3	19	51.7	1.48	257	8.82	324	11.12	42.0	1.440	47.7	1,635
4	21	52.5	1.53	228	8.48	319	11.88	50.5	1.882	43.3	1,612
5	30	53.6	1.44	173	6.19	298	10.70	48.0	1.723	43.5	1,562
6	19	55.6	1.55	146	5.32	305	11.10	46.1	1.678	34.1	1,240
7	24	56.4	1.55	234	8.62	290	10.70	43.4	1.602	44.2	1,635
8	20	57.6	1.56	218	7.88	324	11.68	48.6	1.756	43.7	1,578
9	18	57.8	1.60			264	9.47	40.6	1.460	40.6	1,458
10	25	58.4	1.62			287	10.30	39.2	1.410	40.4	1,452
11	21	59.7	1.66	228	8.50	288	10.78	49.0	1.830	41.7	1,558
12	30	62.1	1.66	216	8.46	318	12.48	54.7	2.145	46.6	1,825
13	32	63.5	1.62	176	6.88	300	11.75	51.1	2.000	43.4	1,700
14	32	65.0	1.66	163	6.52	254	10.17	36.9	1.475	36.1	1,443
15	20	67.2	1.68	225	8.65	317	12.17	45.6	1.752	46.6	1,790
16	22	68.0	1.77			262	10.82	36.7	1.515	40.9	1,688
17	21	71.4	1.73			269	11.23	38.1	1.590	39.5	1,646
18	19	74.3	1.78	171	7.19	269	11.32	46.3	1.946	39.6	1,664
19	22	77.7	1.85	160	6.70	222	9.34			32.0	1,345
20	24	81.5	1.94	117	5.15	240	10.54	39.5	1.736	36.0	1,582
21	23	84.8	1.93								
Median	22	59.7	1.62	181	7.03	287	10.78	45.0	1.700	40.9	1,580
Mean	23	62.8	1.64	190	7.19	284	10.74	44.5	1.676	41.0	1,505
Standard deviation	4.2	10.1	0.14	38	1.25	28	0.98	5.1	0.212	4.0	160

TABLE III. COMPARISON OF NONPREGNANT AND JUST-DELIVERED WOMEN

	MEAN WEIGHT (Kg.)	MEAN SURFACE AREA M. <sup>2</sup>	VOLUMES OF DISTRIBUTION								EXCHANGEABLE SODIUM	
			SUCROSE		4 HOUR NA <sup>24</sup>		T-1824					
			ML./Kg.	L./M. <sup>2</sup>	ML./Kg.	L./M. <sup>2</sup>	ML./Kg.	L./M. <sup>2</sup>	ML./Kg.	L./M. <sup>2</sup>	MEQ./Kg.	MEQ./M. <sup>2</sup>
Nonpregnant	64.0	1.69	169	6.32	254	9.59	40.8	1.530	39.4	1.475		
Just-delivered	62.8	1.64	190.5	7.19	284	10.74	44.5	1.676	41.0	1.505		
Difference	1.2	0.05	21.5	0.87	30	1.15	3.7	0.146	1.6	30		
Standard error of difference	3.3	0.04	11.9	0.385	9.7	0.349	1.97	0.068	1.44	55		
p	>.5	.25	.07	.025	.002	.001	.06	.035	.27	>.5		



cases, as judged by the fact that the volume of distribution continued to increase throughout the periods of observation. Sodium<sup>24</sup> and T-1824 were not always available and this accounts for omission of the relevant measurements in some cases.

The volumes of distribution of sucrose, Na<sup>24</sup> at 4 hours, and T-1824, as well as the 24 hour exchangeable sodium, all averaged somewhat higher in the just-delivered women than in the nonpregnant control subjects. However, the statistical analyses shown in Table III indicate that only the 4 hour sodium space was significantly greater in the just-delivered women than in the controls. The differences between the two groups approached statistical significance in the comparisons of sucrose and T-1824 spaces, especially when these were related to body surface area. The exchangeable sodium was essentially the same in the two groups, despite the significant expansion of the sodium space in the just-delivered women. This is explained by the slightly decreased serum sodium concentrations found in the just-delivered patients (a well-known change in pregnancy).

*Changes in the First Week After Delivery.*—Table IV summarizes the changes observed from immediately after delivery to the seventh day post partum. Patients 16 and 17 were uncooperative and their balance studies

TABLE IV. CHANGES FROM IMMEDIATELY POST PARTUM TO THE SEVENTH DAY AFTER DELIVERY

CASE NO. (TABLE II)	WEIGHT CHANGE (Kg.)	CHANGES IN VOLUMES OF DISTRIBUTION			CHANGE IN EX- CHANGE- ABLE SODIUM (mEq.)	SODIUM BALANCE (mEq.)	POTAS- SIUM BALANCE (mEq.)	CHANGE IN SERUM SODIUM (mEq./ L.)
		SUCROSE (L.)	4 HOUR NA <sup>24</sup> (L.)	T-1824 (L.)				
1	-2.2		-1.3	-0.030	-210	- 69	102	0
2	-0.3	0.62	-0.5	-0.125	265	- 2	25	8
4	-4.1	-3.84	-3.9	-0.090	-550	-265	33	1
6	-3.7	0.95	-0.2	0.180	- 95	-100	45	3
10	-1.4		-1.9	-0.635	-160	- 53	281	2
11	-3.3		-2.5	0.200	70	-151	87	0
12	-2.7	-4.43	-1.9	-0.450	- 80	-184	38	5
13	-5.2	-3.00	-4.6	-0.695	-690	-425	- 7	1
16	-3.9	-3.15	-2.8	0.355	-365			1
17	-2.2		-0.6		40			6
18	-4.3		-3.4	-0.130	-305	- 87	167	-1
Mean	-3.0	-2.14	-2.15	-0.142	-189	-148	86	2.4
Standard deviation	1.36	2.12	1.38	0.327	265	122	85	2.7
Percentage with de- creases	100	67	100	70	73	100	11	9

were discarded because of incomplete urine and stool collections. All patients lost weight (average 3.0 kilograms) and had contractions in the volumes of 4 hour Na<sup>24</sup> distribution (average loss of 2.15 L.). The sodium balance was negative in all 9 valid cases and the 24 hour exchangeable sodium decreased in 8 of the 11 women. The average sodium loss was 189 mEq. as measured by isotopic dilution and 148 mEq. as measured in the balance studies. Comparisons of the volumes of sucrose distribution were possible in only 6 women because equilibrium was not established in one measurement or the other in 5 cases. Four of the 6 showed decreases in the first postpartal week. The average decrease in the volume of sucrose distribution coincided with that for Na<sup>24</sup> but this appears to be fortuitous, for different numbers of patients

were averaged to get these means. Eight of the 9 patients with balance studies retained potassium. With the exception of Case 2, the smaller the potassium retention, the greater the sodium loss. The changes in plasma volume (T-1824) were usually slight, with decreases occurring in 7 of 10 patients. The serum sodium concentration increased by an average of 2.4 mEq. per liter and only one patient showed a decrease. This is a reversal of a change seen in pregnancy.

*Sodium Changes in and Beyond the Sucrose Space.*—The volume of sucrose distribution, at equilibrium, has been proposed as, but not proved to be, a measure of the extracellular fluid volume.<sup>3</sup> It is of interest, therefore, to see what the early puerperal changes in exchangeable sodium were in the sucrose space (extracellular fluid?) and beyond it (cells and bone?). Table V indicates that there were no consistent changes in either compartment. In

TABLE V. EARLY PUERPERAL CHANGES OF SODIUM IN AND BEYOND THE SUCROSE SPACE

CASE (TABLES II AND IV)	SODIUM IN SUCROSE SPACE			SODIUM BEYOND THE SUCROSE SPACE				
	JUST AFTER DELIVERY (mEq.)	7 DAYS AFTER DELIVERY (mEq.)	CHANGE (mEq.)	JUST AFTER DELIVERY		7 DAYS AFTER DELIVERY		CHANGE (mEq.)
				AMOUNT (mEq.)	FRACTION OF TOTAL (%)	AMOUNT (mEq.)	FRACTION OF TOTAL (%)	
2	1,020	1,165	145	965	48.6	1,085	48.3	120
4	1,875	1,350	-525	625	25.0	600	30.8	-25
6	1,335	1,500	165	1,085	44.8	825	35.5	-260
12	1,960	1,390	-570	630	24.3	1,120	44.7	490
13	1,920	1,510	-410	1,040	35.2	760	33.5	-280
16	2,140	1,710	-430	1,020	32.3	1,085	38.8	65
Mean	1.708	1.437	-271	894	34.3	912	38.9	18

4 of the 6 cases there were losses of sodium from the sucrose space, but in 2 there were gains. Sodium beyond the sucrose space increased in 3 and decreased in 3 cases. The proportion of exchangeable sodium occurring beyond the sucrose space varied from 25 to 48.6 per cent just after delivery; 7 days later the range was from 30.8 to 48.3 per cent. There was no consistent trend for the proportion increased in 3 and decreased in 3 instances. In 11 of the 16 nonpregnant women the proportion of exchangeable sodium beyond the sucrose space ranged from 31.2 to 49.1 per cent; in one it was 13 per cent (error?). Data were not obtained for the calculation in the remaining 4 cases.

### Comment

The classical argument for hydration of maternal tissues in pregnancy consists of four interrelated observations made in the early puerperium and interpreted as representing a reversal of changes that had occurred during pregnancy. These are: (a) postpartum diuresis,<sup>6</sup> (b) postpartum weight loss,<sup>1</sup> (c) the atonic and flaccid condition of the skin after diuresis,<sup>1</sup> and (d) the shrinkage in diameters of the neck, arms, and legs.<sup>7, 8</sup> Most of the observations were made in the latter half of the nineteenth century, at a time when puerperal women were kept in bed for 2 weeks, starved for the first 2 or 3 days, and allowed only a soft, bland diet for the next week or so. Moreover, dietary sodium was not restricted in the antepartal period in that era.

The postpartum diuresis was not impressive in the women of the present series. In 72 patient-days (9 patients, each observed for 8 days) the 24 hour

urine volumes exceeded 2,000 ml. on only 6 days. One patient excreted 2,515, 2,610, and 2,340 ml. on the first, second, and sixth days, respectively, but lost only 0.3 kilogram in body weight. Two patients excreted over 2,000 ml. on the first day and one did so on the second day after delivery. Hutchinson, Plentl, and Taylor<sup>9</sup> and Haley and Woodbury,<sup>10</sup> who measured total body water by dilution of deuterium oxide, did not find marked net losses in the early puerperium. They did find that the water turnover rate was increased; the higher urine volume outputs were nearly balanced by augmented fluid intakes.

These same investigators made serial measurements of total body water in a total of 9 normal pregnant women. The average rate of water gain in the last two trimesters was 235 ml. per week. Ignoring gains that may have occurred in the first trimester, this would amount to 6.3 L. gained in the last 27 weeks of gestation. Table VI shows that all but 0.7 L. of this can be accounted for in the conception product and growth of the uterus and breasts.

TABLE VI. WATER GAINED IN PREGNANCY

	AVERAGE WEIGHT (GM.)	AVERAGE WATER CONTENT (%)	AVERAGE VOLUME OF WATER (L.)
Fetus	3,200 <sup>11</sup>	75 <sup>12, 13</sup>	2.4
Placenta	500 <sup>11</sup>	83 <sup>14</sup>	0.4
Amniotic fluid	800 <sup>15</sup>	99	0.8
Uterine growth	1,200 <sup>16</sup>	71*	0.9
Breast growth	1,500 <sup>17</sup>	71*	1.1
Total			5.6

\*Assumed.

The well-known expansion of the maternal blood volume calls for about 1.3 L. of water,<sup>1</sup> some of which is gained in the first trimester. These calculations are all based upon averages of data that vary widely, but on the average there appears to be no evidence for the hydration of maternal tissues in normal human pregnancy. This is in agreement with findings in dogs and guinea pigs.<sup>1</sup>

The weight losses in the puerperium are not so striking in modern studies as in the older reports. Stander and Pastore,<sup>18</sup> in 1940, reported on the largest series ever studied. In 2,500 normal women they found an average weight loss of 2.3 kilograms in the first 10 days after delivery.

*Extracellular Fluid Volume.*—There are several physiologic changes in pregnancy that might be expected to increase the extracellular fluid volume. Notable among these are: (a) the increase in venous and, therefore, capillary pressure in the legs,<sup>19</sup> which make up 37 per cent of the body weight,<sup>20</sup> (b) a reduction of about 20 per cent in plasma oncotic pressure,<sup>1</sup> and (c) the allegedly marked retention of sodium throughout pregnancy, as found in all reported balance studies.<sup>1</sup>

While no dilution method has been completely validated as measuring the extracellular fluid volume, the volumes of distribution of inulin, sucrose, and mannitol have been proposed as approximations. The average loss in the volume of sucrose distribution, from immediately post partum to the seventh



day after delivery, averaged 2.14 L. Perhaps this represents a reversal of the gain during pregnancy. If so, it is of just about the right magnitude to be expected from another devious calculation based upon averages.<sup>1</sup> Goudsmit and Louis<sup>21</sup> found that a decrease of 1 Gm. per 100 ml. in serum proteins results in an increase in thiocyanate-available water amounting to  $3.8 \pm 0.8$  per cent of the body weight. In normal pregnancy the serum proteins do drop by an average of 1 Gm. per 100 ml.<sup>1</sup> The average pregnant woman gains from 59 to 69 Kg.<sup>1</sup>; thus the expected increment in available water would be about 2.6 L. While thiocyanate measures more than extracellular water, this increment might represent interstitial fluid gain.

**Body Sodium.**—Gray and Plentl<sup>22</sup> made serial measurements of the 24 hour exchangeable sodium in 10 pregnant women and found that the increments in the second and third trimester averaged 500 mEq. (in the 6 women who remained wholly "normal" throughout pregnancy). This amount could be accounted for in the conception product and expanded maternal plasma volume and most of the retained sodium is delivered by the obstetrician. If the older balance studies were correct, the allegedly large amounts of sodium stored must be nonexchangeable with  $\text{Na}^{24}$ . Also, such stored sodium must be osmotically inactive, for if held in isotonic solution, water gains of from 19 to 105 L. would be required.<sup>1</sup>

The measurements of exchangeable sodium made immediately after delivery, in the present study, were not significantly different from those made in nonpregnant women by us, or by other investigators (Table VII). The

TABLE VII. EXCHANGEABLE SODIUM IN NONPREGNANT WOMEN

AUTHOR	CASES	SODIUM (mEq./Kg.)
Forbes and Perley <sup>23</sup>	7	39.5
Miller and Wilson <sup>24</sup>	6	42.3
Edelman, James, Brooks, and Moore <sup>25</sup>	4*	40.9
Ikkos, Luft, and Sjögren <sup>26</sup>	4	37.7
Klein and Carey <sup>27</sup>	20	39.2
Present series	12	39.4
Mean	53	39.4
Standard deviation		3.5

\*Excluding 2 obese women.

losses of sodium in the first week of the puerperium averaged 189 mEq. as measured by the tracer method and 148 mEq. as measured in the balance studies. These data are in accord with the average negative sodium balance of 212 mEq. that Taylor, Warner, and Welsh<sup>28</sup> found in the first 10 days after delivery, in 3 normal women. These losses are not great enough to match the loss of water from the sucrose space, if this is assumed to be extracellular water. This fact would suggest that some small amount of sodium may move out of the cells or bone in the week following delivery. In 3 of the 6 cases shown in Table V this apparently happened, but there are too few cases to build an argument upon.

**Plasma Volume.**—All investigators of the subject have found that the plasma volume increases significantly in pregnancy.<sup>1</sup> In the present study



the plasma volumes of the just-delivered women were not significantly different from those of nonpregnant women and the decreases in the first week of the puerperium were slight. There are two reasons for this apparent disagreement with all previous findings. The plasma volume may decrease in the last weeks of pregnancy,<sup>29</sup> although not all investigators agree.<sup>30</sup> Tatum<sup>31</sup> has found abrupt changes in the plasma volume such that "within two hours after delivery, the plasma volume decreased in the majority of patients to a level lower than has been reported for any time during the last half of pregnancy."

*Validity of the General Approach.*—Can one use just-delivered women as representing "pregnant" women without their pregnancies? Labor and delivery do distort the plasma volume and for this particular measurement the answer to the question obviously is no.

The measured volumes of sucrose distribution, immediately after delivery, may be close to the maternal sucrose space before labor. The average loss of 2.14 L. in the first week after delivery can be related to measurements of the mannitol space made in pregnancy. Seitchik and Alper<sup>32</sup> made such serial measurements in 7 normal pregnant women and found an average gain of 125 ml. per week, from the eighth to the thirty-seventh week. By extrapolation, the total gain, from the eighth week to term, would average 3.95 L. They stated that the infusions were continued until equilibrium was attained, which suggests that fetal fluids available to mannitol had also come into equilibrium. Calcagno, Husson, and Rubin<sup>33</sup> found that the volume of inulin distribution in newborn infants averages 346 ml. per Kg. In a 3,200 gram fetus with a 500 gram placenta, the fluid available for mannitol distribution would average about 1.3 L. An unknown portion of the amniotic fluid might also be included in the measurement but, without this, the total gain of 3.95 L. minus the 1.3 L. in the fetus and placenta would leave 2.65 L. as an estimate of the increment to the maternal tissues. This is in fair agreement with the decrement in sucrose space that occurs in the first week after delivery and both figures check well with the increase to be expected in pregnancy, as was calculated above.

The data for exchangeable sodium are wholly consistent with the measurements that Gray and Plentl<sup>22</sup> made in pregnant women.

### Summary and Conclusions

Dilution methods were applied in the comparison of 21 normal, just-delivered women to 16 nonpregnant "hospital normal" women who were selected to match the former group in respect to body weight and surface area.

The volumes of distribution of T-1824, sucrose, and  $\text{Na}^{24}$  at 4 hours averaged slightly higher in the just-delivered women than in the controls. However, only the 4 hour  $\text{Na}^{24}$  space showed a statistically significant difference.

The 24 hour exchangeable sodium was essentially the same in the two groups of women.

Eleven of the just-delivered women were kept on a balance study for 7 days, at the end of which time the measurements were repeated. The sucrose and 4 hour sodium spaces each decreased by about 2 L. Only slight decreases were found in the plasma volumes and 24 hour exchangeable sodiums.

It is suggested that normal pregnancy is not accompanied by a significant hydration of the maternal tissues, or by a storage of exchangeable, osmotically active sodium in the mother.

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## EMOTIONAL FACTORS IN TOXEMIA OF PREGNANCY

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**D**ESPITE great advances in the field of obstetrics, the toxemias of pregnancy still complicate some 6 to 7 per cent of all gestations.<sup>17</sup> Their cause, "despite decades of intensive research, remains the great enigma of obstetrics and constitutes one of the most important unsolved problems in the field of human reproduction."<sup>12</sup>

This paper represents a résumé of a study of toxemia patients conducted during the past 5 years at Harlem Hospital. The word toxemia is here applied only to (1) pre-eclampsia, (2) eclampsia, and (3) hypertension arising after the fourth month of pregnancy.

From the outset, it was noted that the toxemic women were an unhappy group. At first, it was assumed that this state of unhappiness was induced by the illness. Since pregnancy is usually accepted as a normal part of life, it was some time before it was recognized that it was the pregnancy itself that was causing these patients to feel unhappy. This led to a review of the previous work done on the relation between the emotional state of pregnant women and toxemia. There is a general impression<sup>8, 9</sup> that toxemia was more common in "neurotic women." No detailed studies were ever carried out, however.

During the attempt to learn the cause of the unhappiness in these toxemic patients, it became evident that pregnancy had a different meaning to different women. This "meaning of pregnancy" serves as one of the bases for this study.

It is known that toxemia of pregnancy is rare in some African countries while it is very common among American Negroes.<sup>10-11, 14</sup> Also, in many of the other so-called uncivilized areas of the world, such as among the Eskimos of Greenland and certain tribes of the South Pacific, there is little or no toxemia.<sup>10, 13, 23-25</sup> In other words, there seems to be a "nontoxemic world," although widely scattered about the globe.

The scarcity of this disease in the "nontoxemic world" is mentioned by Dieckmann<sup>10</sup>: "Our data seem to indicate," he writes, "that toxemias of pregnancy, especially eclampsia, are diseases of culture and civilization, probably because of the mental strain and stress, and changes in diet and habits."

With the "meaning of pregnancy" as the common denominator, a comparative study was made among the women of our civilization and the women of the "nontoxemic world."



### The Meaning of Pregnancy in Primitive Societies

The data for this part of the study were obtained through the extensive literature concerning the customs of these people and through personal communication with physicians and other trained observers who have lived and worked among them.<sup>2-5, 7, 13, 16, 18-20, 23-28, 32, 34-37, 39-40</sup>

The following summarizes the customs and attitudes toward motherhood. In all the communities where pre-eclampsia is rarely or never seen, women have a particularly important place. They feel that the survival of the group is dependent upon them. They feel at ease in this, as well as in any other tasks necessary for the existence of the tribe. Besides this, pregnancy and delivery are joyful events to all. In some places a party is given, or neighbors will drop in while the woman is still in labor to touch the unborn baby for good luck. A pregnant woman is handled with extreme tenderness and love. In Nigeria she is treated like a heroine and receives gifts from husband, parents, and friends. Marriage is not essential in some of these groups.

On the other hand, conception is of the utmost importance and barrenness is a disgrace, even signifying "ties with the evil one." The infertile woman feels inferior and is so regarded. A woman is judged by the number of children she has. It reaches a point where a mother of five, married or not, feels she is a better woman than the mother of only two. The woman who has had children will be entitled to a higher dowry when she does marry than a woman who has borne none. Infertility is a major cause of divorce, and the man has the right to take the woman back to her parents. This applies even where the male is responsible for the infertility, although he has no idea of it.

Throughout Africa and the other primitive groups studied, babies of both sexes are welcome. In times of famine it is customary among the Eskimos to kill the children and the elderly. Women are expected to procreate as soon as the danger is over, and they do their part willingly. In the parts of Africa where Westerners have exerted little or no influence, the women have no fear of childbearing. The same applies to the Greenland Eskimos and the Island Territory of the South Pacific. As for children born out of wedlock, there is no stigma attached to them.

Thus the meaning of pregnancy in these primitive societies becomes apparent. Procreation signifies the key to the survival of the group. "The highest sacrifices are made for the fertility of the crops." Fertility is cherished by both men and women, young and old.

### The Meaning of Pregnancy in Our Culture

In our complicated civilization, the meaning of pregnancy is not at all as easy to arrive at as in simpler societies. When a woman is pregnant, it soon becomes apparent to all about her. But what are the inner feelings of the pregnant woman toward her condition? Will the pregnancy stimulate forces of love and hope and faith, or will it ignite the forces of self-destruction? These opposing emotions are accepted as an integral part of the psychological make-up of all human beings.<sup>15, 21, 31</sup> Will the pregnant woman regard gestation, labor, and delivery as one joyful process of procreation? Will she be willing, as well as emotionally and physically able, to cope with the responsibilities of pregnancy? Or will her own pregnancy, because of the circumstances in which she finds herself, signify deceit, shame or "sin," feelings that will evoke her destructive forces?

In the answer to these questions lies the "meaning of pregnancy" in our culture.

In order to obtain these answers an interviewing technique was gradually devised to elicit answers to the following questions: Did you wish to



become pregnant? Do you still wish to remain pregnant? Were you prepared for the inevitable social, economic, and physical demands of the pregnancy? Does it mean trouble with which you cannot cope? Does the pregnancy bring you happiness? How do you finally accept all that goes with pregnancy, labor, and delivery? In other words, do you feel that it is worth while? Or are you just going through with it because your mother or friends did, or because your husband wants children? Do you regard your unborn baby as an individual, or do you think of yourself and the child as being one?

The actual questions asked of the patients were, of course, worded very simply so that the patient could readily understand.

### Clinical Material at Harlem Hospital

In Harlem Hospital 43 patients with toxemia and 69 patients without toxemia were studied.

All the patients had more or less the same environment; 109 were Negro, one was white, and 2 were mixed (Puerto Rican).

Table I gives the types of toxemia found in this study.

Tables II, III, and IV give the marital status, parity, and associated conditions of both groups. It should be noted that there were no significant differences between the toxemic patients and the control group in regard to these factors.

TABLE I. TYPES OF TOXEMIA

Pre-eclampsia	27
Eclampsia	2
Hypertension alone	14
Total	43

TABLE II. MARITAL STATUS

	MARRIED	SINGLE	SEPARATED	TOTAL
Toxemia group	18	20	5	43
Control group	38	26	5	69
Total				112

TABLE III. PARITY

	TOXEMIA GROUP	CONTROL GROUP	TOTAL
Primiparas	27	31	58
Multiparas	16	38	54
Total	43	69	112

TABLE IV. ASSOCIATED CONDITIONS

TOXEMIA GROUP	CONTROL GROUP
Previous toxemia 2	Previous toxemia 3
Drug addiction 1	Drug addiction 2
	Hyperemesis throughout pregnancy 3
	Excessive weight gain 3

Table V summarizes the result of the interviews employed to determine the "meaning of pregnancy." This table has been greatly curtailed of necessity because of the large amount of material gathered in the course of the interviews.

TABLE V. SUMMARY OF DATA FROM INTERVIEWS TO DETERMINE MEANING OF PREGNANCY

ATTITUDES TO PREGNANCY	TOXEMIA GROUP			CONTROL GROUP		
	PRESENT	ABSENT	NOT RECORDED	PRESENT	ABSENT	NOT RECORDED
Wished to become pregnant	40	1	2	66		3
Ambivalence toward wish to remain pregnant	25	10	8	1	63	5
Ability to cope with responsibility of pregnancy	11	31	1	58	9	2
Willingness to cope with the responsibility of pregnancy	14	18	11	60	4	5
Procreation considered synonymous with womanhood	16	14	13	50	6	13
Pregnancy signifies deceit, shame, or "sin"	30	5	8	5	55	9
Trapped by the pregnancy but without bad feelings	9	29	5	15	25	29
Feeling toward pregnancy—good	3	29		53		
Feeling toward pregnancy—downcast	27	5		1		
Feeling toward pregnancy—mixed	11		1	14		1
Pity for self and women in general	29	4	10			
Anger with men	25	2	16	7	49	13
The male does not want the pregnancy	15	4	16	18	23	28
Environment hostile to pregnancy	39	3	1	36	28	5
Guilt toward unborn baby	33	7	3	4	60	5

It is noted that except for the wish to become pregnant, the toxemic patients' attitudes to pregnancy differed greatly from those of the control group. The following case histories illustrate some of the differences.

CASE 1.—B. D., aged 20, attended the Prenatal Clinic and had an uneventful antepartum course. This was her first pregnancy. She had old burns on the lower abdomen and the right thigh, and strabismus of the left eye. The patient was single and for that reason she was "disgusted" in the first 2 months. She felt happy later because "I wanted it, that's why."

The father of the baby wanted the pregnancy also and he brought the patient to the hospital when she went into labor.

Patient felt no inner pressures, never felt that she would like to get rid of the pregnancy, never blamed the pregnancy (the baby). She blamed herself for getting pregnant before her marriage. She did not feel bad about it, however, and she planned to get married the next month. She loved her future husband and felt that the love was mutual. She also felt that she is a happy person in general. She loved children but both she and her future husband planned to have only two babies because they did not think that they could provide for more. The patient thinks that a woman should have babies. For her, "that's it." As far as plans for the future were concerned, she already had an apartment and was preparing for marriage.

CASE 2.—H. J., aged 21, pregnant with her first child, was admitted to the Obstetrical Department in December, 1953. When first interviewed she had headaches, occasional spots before the eyes, moderate edema of the feet, 4 plus albuminuria. The blood pressure was 190/110 and she was 6 months pregnant.

The patient was shy throughout the interviews. Her language was that of a child, with many grammatical errors, particularly when touching upon a subject that implied a feeling of guilt about the baby. She had married the father of the baby when she was 2 months pregnant.

The interviews showed that this patient had an ambivalent attitude toward gestation as a whole. At times she felt that she wanted the pregnancy and at other times she

did not want it. She would be "ashamed if the baby knew about this." She was not sure whether or not she wanted to know anything about labor. She felt unable to cope with the pregnancy believing that she would not be able to go through labor. At one point she said that she wished the pregnancy could be carried "outside, because it would be easier to carry." Again and again she expressed the feelings of sinfulness and that pregnancy out of wedlock could make her sick.

The patient was given the routine pre-eclampsia treatment. During the interviews in the hospital labor and delivery were explained to her. After 11 days the blood pressure was still 142/80 and there was 1 plus proteinuria. She signed herself out of the hospital, stating, "I feel much better inside. I guess I am getting to understand a little better how to work it out."

Two weeks later she was readmitted in false labor. The blood pressure this time was 142/90 and there was 3 plus albuminuria. Several days later she went into labor and was delivered of a live 2 pound, 11 ounce baby. The blood pressure the following day was normal.

In the first case, despite illegitimacy, the woman enjoys pregnancy and wishes more babies. Pregnancy brings out constructive feelings. In the second case there is a conflict between the desire for pregnancy and the feelings of sin and the inability to carry the pregnancy through.

These latter feelings were found to be characteristic of the toxemia patients.

### Comment

Among the patients observed, pregnancy had different meanings. To many it was a wonderful or happy event. To others it meant unhappiness, difficulties in adjustment, humiliation, and even obscenity.

There was often an implied feeling of sin. Furthermore, in some of these patients procreation was not always an instinctively satisfying and happy experience. Many of these women felt they had no place in the community. All this is in contrast to the meaning of pregnancy in the so-called primitive or "nontoxemic world."

The women studied here may be divided into three main categories, based upon their reactions to the pregnancy.

The first type consists of those who react in a mature way to the pregnancy. For them procreation is not only the primary function of womanhood but it is borne with relative ease. Even though they may live in a hostile environment and are pregnant out of wedlock, they are quite able to go on without a break in health. They welcome procreation and because of this they are fit for almost any eventualities. They adjust with ease. When one of this type finds herself pregnant out of wedlock, she is not thrown into despair and filled with a sense of guilt. She is able to exercise her function of procreation first and foremost and will not find herself entertaining thoughts of punishment. She wanted a baby and can still go out and look for a husband or a job and build a future.

The second type is made up of women who have no idea of what their responsibilities are. Procreation is regarded as more of a curiosity than a fulfillment. Pregnancy may be looked upon as a game and the burden of the pregnancy and the care of the offspring are shifted onto the mother or relatives. Such a woman is only slightly involved in what is happening and therefore feels neither good nor bad about it. As long as the baby is taken care of, even if only by a good friend instead of by herself, all is well. This type is more prevalent among the younger teen-agers, and is called the "little-girl type."

The third type consists of the women who develop toxemia of pregnancy. One of the characteristics of this group is an ambivalence to the pregnancy.



She wants the pregnancy to prove she is a woman. However, she uses every external situation as a reason for not wanting the pregnancy. For example, such a patient pregnant out of wedlock gives the impression that she is suffering deeply because she has broken certain strict rules of society, in contrast to the mature woman who may enjoy the pregnancy. She may complain about lack of adequate housing and poverty. But even in some of our cases where we did arrange for improved housing and economic relief the attitude toward the pregnancy remained unchanged. The toxemic woman apparently does not have the capacity to enjoy pregnancy even under the most favorable circumstances.

These women manifest a basic feeling of inferiority especially relating to sex and procreation. This was borne out in many interviews. Because of this feeling of inferiority, the patient's ideals concerning pregnancy may be of the highest order, to include marriage, a nice home life with the male, proper housing and finances, and a superior physical stamina. She is filled with guilt upon the slightest infringement upon her phantasies. Her inferiority concerning procreation is exposed by the pregnancy. She identifies (feeling like "one") with the unborn baby. This way she judges her defects as if the baby were judging her. Thus she will state, "I would be ashamed if the baby knew." A strong feeling of guilt in the eyes of the baby is so developed. This identification is particularly strong at the end of the pregnancy.

Some of these patients are dimly aware of their distorted attitudes toward sex and reproduction. Others lack any insight in the matter and do not realize that they are complaining about their own lack of "feeling like a woman." Such a patient is trying to hide her conflict and cannot admit it even to herself. With combination of personality defect, unfavorable forces in the environment, and the pregnancy itself, the patient of toxemic makeup undergoes a critical and acute loss of self-esteem. This results from the feeling of guilt in the eyes of the unborn baby mainly because she finds the pregnancy a heavy task and she feels "unable to do a good job of it." This feeling of guilt triggers destructive forces in the woman with the toxemic makeup. She feels bitter, overly fearful of pain and death. Anger and hate make her feel as if she were "going to burst." She directs these destructive emotions against herself.

Psychiatry has shown that the "Don Juan," the "ulcer" patient, the neurotic, the schizophrenic, and other types are each using their particular device to cover up or simultaneously express hidden and deep-seated intrapsychic conflicts. Unable to admit their inner defects, even to themselves, these individuals develop these different defense mechanisms. Painful and destructive as some of these may be, still they afford the individual the possibility of feeling himself more acceptable to the world around. These defenses enable the personality to adjust to life and to survive, in spite of the unresolved problem.

It is suggested that toxemia of pregnancy is such a defense mechanism. One can see and help the toxemia; none should know of the patient's inner defect, not even the patient herself, for this is far more painful and unacceptable to her than is the toxemia.

The following diagram is an attempt to summarize the proposed mechanism of the development of toxemia:

1. Personality defect + pregnancy = Distortion of the normal meaning of pregnancy
2. Distorted meaning of pregnancy → Guilt feelings → Stimulation of destructive forces  
Need for defense mechanism → Toxemia of pregnancy.

*Defense Mechanisms: Somatic and Psychological.*—Thus it can be seen that toxemia is looked upon as one pattern of defense brought on by the pregnancy in a certain type of personality. In order to test the validity of this



hypothesis, a study of schizophrenic pregnant women was made. The schizophrenic woman has already developed her own characteristic pattern of defense,<sup>1</sup> and pregnancy should not evoke the chain of reactions set down above.

A questionnaire was sent to a number of psychiatric institutions. In 730 cases of schizophrenic patients delivered in 44 institutions in the United States there were only 2 with pre-eclampsia, and none with eclampsia. Two other patients had chronic hypertensive cardiovascular disease. In 34 schizophrenic patients from Brazil and 3 from Canada, there were none with pre-eclampsia or eclampsia. Thus in 767 pregnant schizophrenic patients there were only 2 cases of pre-eclampsia.

These patients, when not hospitalized, have no dietary restrictions during pregnancy. Even in the institutions, these patients manage to obtain as much salt as they desire, from other patients or visitors.<sup>6, 29, 33</sup> It is very difficult to maintain them on a salt-poor diet. In schizophrenic patients, at least, salt does not seem to be associated with toxemia.

A case was recently reported that seems to bear out some of these thoughts.<sup>38</sup> The patient had been schizophrenic since 1938, during which time she had had two normal pregnancies. In 1952 a frontal lobotomy was performed and "resulted in a great improvement in her psychosis." In 1956 she developed severe pre-eclampsia during a third gestation. As a woman with severe schizophrenia she had a set pattern of defense. When she improved after the lobotomy, a different defense pattern was able to develop—pre-eclampsia.

Fourteen of the institutions replied that cases of toxemia were not seen in any of their patients, including those with mental disease other than schizophrenia. These results may be significant enough to warrant a more comprehensive investigation which would include mental illness, other than schizophrenia, which was selected for the present study.

There has been no attempt here to explain why certain conditions are commonly found associated with toxemia, such as multiple pregnancies, hydatidiform mole, and primiparity. As far as primiparity is concerned, a possible explanation may be derived from the material gathered here, and from later studies. It seems that the experience gained through the first pregnancy will equip the patient to handle herself better in subsequent gestations. The proof of this thesis is beyond the scope of this present paper, and it is intended that it will be presented in a future report. The relationship of tuberculosis and toxemia of pregnancy is another subject for investigation for it has been found that the incidence of toxemia is low in tuberculosis patients. The same applies to women suffering with hyperemesis throughout gestation.<sup>30</sup>

### Summary

In an attempt to ascertain the role played by emotional factors in the etiology of toxemia of pregnancy, a comparative study has been made between the "meaning of pregnancy" to so-called primitive peoples, and to a group of patients observed in our culture.

It is postulated that the "meaning of pregnancy" is the result of the interaction between emotional attitudes toward sex and procreation, and reactions to the environmental forces at the time of procreation.

In the primitive cultures, pregnancy has a happy meaning and the incidence of toxemia is very low or nonexistent. In the patients studied here, the "meaning of pregnancy" is not uniform. In those with a certain personality defect regarding sex and procreation, pregnancy will have an unhappy meaning. These patients find themselves unable to carry the pregnancy with ease.

They feel guilty in the eyes of the unborn baby and sense that the baby is judging their inability. This in turn stimulates the destructive forces latent within the woman. Toxemia of pregnancy is one manifestation of these destructive forces—the result of self-judgment and self-punishment.

To test the validity of this hypothesis a study of pregnant schizophrenic patients was made. These patients have a pre-established pattern of defense. Toxemia was found to be very unusual in them. Schizophrenia is a mental solution while toxemia represents a somatic solution to conflict.

If the psychological factors likely to produce toxemia can be detected early in the patient's prenatal course, and opportunities provided for her to express herself about the pregnancy, this may well facilitate prophylaxis of toxemia.

Finally, regardless of the interpretation of the specific nature of the psychological factors, the data here strongly suggest that the emotional conflict arising from pregnancy plays an important role in producing toxemia.

It is felt that further investigation along these lines is certainly indicated.

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## SOCIAL FACTORS IN THE PREDICTION AND TREATMENT OF EMOTIONAL DISORDERS OF PREGNANCY

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SOCIAL scientists have presented in the recent sociological and psychiatric literature many studies relating social and environmental factors and emotional disorders.<sup>2, 3, 11, 13, 15, 17-23</sup> Reports indicated that social factors may have importance in the emotional disorders of pregnancy and childbearing.<sup>1, 4-10, 12, 14, 16, 24</sup> These have led to a consideration of the possibility of predicting maternity patients' emotional reactions from social history to help the physician better to recognize potentially ill patients. Moreover, if social factors were related to the onset of the disorder, perhaps efforts at alleviating them might assist patients in recovering once the illness had developed. If this were possible practitioners might more effectively treat this group of illnesses.

Psychiatric maternity patients, as do many other psychiatric patients, often have in their social histories more family history of emotional disorder, divorce and separation, and homes broken by death of a parent than do normal controls. They may have a greater tendency to serious physical illnesses than normal individuals, a tendency to marry husbands either much older or somewhat younger than themselves, and they often have older parents than do normal persons.<sup>3, 8</sup> Psychiatric maternity patients, however, may differ from normal patients and other young married psychiatric female nonmaternity patients in that: they may have a higher incidence of previous personal emotional disorders, they are often 33 years of age or older at the time of emotional upset, they have more physical complications of pregnancy, and they have unplanned pregnancies. They more frequently have recently made a change of residence, their husbands often are unavailable in the weeks after the baby's birth, and they receive less help in the first weeks after return home from the hospital.<sup>7, 8</sup> Educationally more of the psychiatric maternity patients have had some college education (32 per cent as compared to 13 per cent of comparable nonmaternity married young women psychiatric patients, and 8 per cent of married women in the general community according to the 1950 census) but very few have completed college (21 per cent of both groups of women psychiatric patients, as compared to a census figure of 49 per cent of the community's women population) ( $p < .01$ ).

In this paper data are presented on these two aspects of the problem of social factors in pregnancy: (1) a study in predicting a group of women's



emotional reactions to pregnancy on the basis of social history data, and (2) experiences with a modified psychiatric approach in which particular emphasis is placed upon trying to improve the patient's social adjustment to the role of motherhood.

### 1. Prediction of Women's Emotional Reaction to Pregnancy

*Procedure for Prediction Study.*—A social history questionnaire was given to each of 98 normal new mothers consecutively delivered of normal babies at the Englewood Hospital. Four months after delivery the physicians who delivered these women and administered their postnatal care submitted a rating on a four point scale as to the degree of emotional disturbance with which the patients reacted to the maternity experience. On the basis of previous studies it was expected that patients who were judged to show emotional disturbances would give background social histories with quantitatively greater numbers of stressful life experiences than would patients who showed no emotional disturbance.<sup>8</sup> Each patient received a prediction score of from zero to ten which was the total of the number of stressful life experiences in her history.

In addition to comparing social history data in normal women who have undergone various degrees of emotional reaction, data are also included for contrast, when available, from the histories of a group of 55 obstetrical patients whose emotional disturbances were severe enough that they sought psychiatric help. These patients have had mild, moderate, or severe disorders, as classified in a previous paper.<sup>8</sup> Social history data may be grouped in six broad categories which are shown in Table II with the specific items in each group.

For statistical clarity chi-square determinations were made and probability of occurrence by chance is presented in parentheses when indicated.

TABLE 1A. FREQUENCY DISTRIBUTION OF 98 NORMAL MATERNITY PATIENTS' SOCIAL HISTORY PREDICTION SCORES COMPARED TO THEIR EMOTIONAL REACTIONS TO CHILDBEARING

SOCIAL HISTORY SCORE	AMOUNT OF EMOTIONAL UPSET (%)			
	NONE	SLIGHT	MUCH	TOTAL
0-2	22	3	0	25
3-4	40	4	3	47
5-6	7	6	6	19
7-10	2	3	4	9
11-	0	0	0	0
Total	71	16	13	

TABLE 1B. FREQUENCY DISTRIBUTION OF 55 PSYCHIATRIC MATERNITY PATIENTS' SOCIAL HISTORY SCORES COMPARED WITH THE SEVERITY OF THEIR EMOTIONAL ILLNESS

SOCIAL HISTORY SCORE	SEVERITY OF EMOTIONAL DISORDER (%)			TOTAL
	MILD	MODERATE	SEVERE	
0-2	0	0	0	0
3-4	4	4	0	8
5-6	11	11	0	22
7-10	4	34	25	63
11-	0	2	8	10
Total	18	51	32	

*Results of the Prediction Study.*—Of the 98 women studied, 29, or 30 per cent, were judged by their obstetricians to show some degree of emotional upset after delivery. This high percentage may be related to the stressful nature of

the particular community studied.<sup>9</sup> Among the 18 women in the group who had attended antenatal classes the figure was even higher, 44 per cent. These women had a higher mean total score of abnormal items (4.2 as compared to 3.5 for the entire group). Their seeking out and attendance at antenatal classes probably is a reflection of the insecurity they felt.

Table IA presents percentages of occurrence of various total scores of abnormal incidents in the social histories of 98 normal obstetric patients. A definite trend appears for patients with few environmental strains to respond without undue emotional upset, while those with many environmental difficulties tend to react with considerable emotional upset. A comparison with Table IB reveals that social strains are even more frequent in the lives of maternity patients who seek psychiatric help. Table IB includes for comparison percentages in a group of 55 psychiatric maternity patients. We note a continuation of the trend described in Table IA for patients with more severe disorders usually to have quantitatively more environmental problems in their backgrounds. It is very evident that the number of abnormal or stressful social events is highly correlated with obstetricians' ratings of normal women's emotional reactions ( $p < .001$ ) as well as with the severity of the patients' disorders ( $p < .001$ ). The latter group have much higher scores on the whole than the former.

TABLE II. INCIDENCE OF VARIOUS SOCIAL STRAINS IN THE LIFE HISTORIES OF 98 NORMAL MATERNITY AND 55 PSYCHIATRIC MATERNITY PATIENTS

SOCIAL HISTORY ITEMS	NORMAL MATERNITY		PSYCHIATRIC MATERNITY (%)	P
	NO EMO-TIONAL UP-SET (%)	SOME EMO-TIONAL UP-SET (%)		
1. Complications of wife's history				
Emotional problems in wife's background	19	43	64	.001
Wife's parents are older	29	43		.05
Wife from family of 4 or more children	23	52	46	.05
Wife is 33 years or older	17	33	34	.05
Wife was previously married	4	10		.30
2. Complications of husband's history				
Emotional problems in husband's background	7	29		.01
Husband's parents are older	30	71		.01
3. Complications of the marriage				
Husband much older or younger than wife	32	43	59	.01
Religious intermarriage	19	29	36	.05
Husband and wife disagree as to woman's place	4	7		n.s.
4. Physical complications of pregnancy	4	18	55	.001
5. Complications with children				
Baby is first child of 35-year-old or older wife	1	14	15	.01
Baby is the fourth or later child	4	14	16	.05
Wife never previously cared for children	3	21		.01
Wife has had trouble with previous children	13	24		.30
6. Recent strains				
No help available	19	29	80	.001
Suburban migration	36	36	47	.20
Recently moved to a new home	32	40	49	.30
Wife cannot drive a car	29	36		n.s.

In Table II are presented some of the important social history items. The percentages of normal patients in the two broad groups, those who experienced some emotional upset and those who experienced none, are presented in the columns on the left. On the right are percentages of psychiatric patients who showed the strains. The figures on the far right are the probabilities of the results occurring by chance. We have compared statistically the psychiatric patients with the nonemotional normal patients when data were available. When data on psychiatric patients were not available statistical comparisons were made between normal patients who showed some emotional upset and those who were "nonemotional." Included is a comparison of the incidence of different events and attitudes in the lives of more and less emotionally upset normal obstetric patients and actual psychiatrically ill maternity patients. The highly significant differences between emotionally upset and unemotional normal patients is striking, as well as the even greater difference between most normal women and those who become psychiatric patients.

## 2. Study of Socially Oriented Psychotherapy

*Procedure for Psychotherapy Study.*—This study compares 70 psychiatric maternity office patients seen from 1953 through 1957 with a control group of 144 other young (18 to 44 years) married nonmaternity psychiatric office women patients seen during the same period. The patients are divided into three groups, those seen in 1953-1954 when treatment was more passive dynamic psychotherapy; those treated in 1955, the transition period; and those seen in 1956-1957, in which the therapist more actively pointed out and encouraged both groups to deal with present-day social forces as well as their deeper psychodynamics. If social forces are more important in the emotional disorders of maternity patients as a group than the disorders of comparable young married women, one should expect a larger response on the part of the childbearing group to the greater emphasis on present-day social factors in psychotherapeutic discussions.

There is an old problem in measuring the results of psychotherapy. Since the subjective responses of patients and optimistic attitudes of their psychiatrists are suspect, an attempt was made to validate these with objective criteria. These include: the number of sessions before discharge from treatment, on the assumption that fewer sessions before remission indicated a more satisfactory therapeutic method; the number of patients seen only once or twice, who did not accept psychotherapy, a decrease in numbers constituting an improved response to the change in treatment; and finally the numbers of patients hospitalized in psychiatric facilities. Thus, if significantly more 1956-1957 psychiatric maternity patients than nonmaternity psychiatric controls continued treatment after the initial one or two interviews, required fewer sessions before discharge, and fewer required hospitalization, the therapists' active emphasis on present-day social problems, and "What can be done about it?" attitude may be considered more successful in the psychiatric maternity group. For mathematical clarification of results as before, chi-square calculations were made and the probability of occurrence by chance were entered in parentheses after each datum reported.

*Results of Therapy Study.*—The results are presented in Table III. Socially oriented psychotherapy in 1956-1957 resulted in higher percentages of success, as subjectively rated, for both maternity patients and other nonmaternity young married women with emotional disorders as compared to more passive psychotherapy in 1953-1954 ( $p < .05$ ). Similarly there were fewer patients of both maternity and control groups who discontinued therapy after one or two visits ( $p < .01$ ). But again the improvement was greater



for the maternity group, although not to statistically significant levels ( $p$  between 0.2 and 0.1). We can see that by every criterion active socially oriented psychotherapy was more successful in the maternity psychiatric group than a less active approach. Moreover, the improvement was less in every instance in the control group of nonmaternity psychiatric cases.

TABLE III. RESULTS OF SOCIALLY ORIENTED PSYCHOTHERAPY

	MATERNITY PSYCHIATRIC PATIENTS		NONMATERNITY PSYCHIATRIC PATIENTS	
	1953-1954	1956-1957	1953-1954	1956-1957
Number of patients	24	36	60	51
Criterion of success:				
Subjectively evaluated	26%	82%	38%	63%
Accepted treatment	56%	86%	55%	69%
Brief therapy	64%	100%	83%	78%
Outpatients (not hospitalized)	57%	100%	87%	86%

The percentage of maternity patients requiring only brief therapy of twenty or fewer sessions of psychotherapy before discharge was increased considerably after introduction of socially directed therapy. Meantime the controls showed no significant change in number of treatments. This finding is particularly important because the mean number of sessions for brief therapy was six, while for more intensive therapy the mean was forty-five sessions.

In 1953-1954 43 per cent of maternity patients were hospitalized and in 1956-1957 none of the psychiatric maternity group of patients ( $p < .001$ ). Comparative figures for the nonmaternity psychiatric patients were practically unchanged. In 1955-1957 100 per cent of the maternity psychiatric patients were treated as outpatients, but only 87 per cent of the nonobstetric psychiatric group ( $p$  near .05).

*Illustrative Case.*—The importance of social and environmental influences in the development and management of the emotional disorders of pregnancy and childbirth may well be illustrated by a typical case history. Social strains are italicized and numbered.

A (1) *24-year-old* housewife of Jewish extraction became depressed 3 months after the birth of her first child (a boy) and sought psychiatric help. She was continually afraid that she might lose control of herself, and "destroy" herself or her baby. She was unable to sleep except on weekends when her husband was home. Her husband, *aged 28*, also of Jewish descent, was an engineer.

The patient was the third and youngest child of a Brooklyn family. Her (2) *mother died* following a hysterectomy at the age of 39 when the patient was 6, her (3) *father died* at (4) *53* when the patient was 12. Her stepmother left her in the care of her 18-year-old sister of whom the patient was quite fond.

The patient completed high school and (5) *a year of college* at night. She enjoyed sports, an active social life, the theater and ballet. She held the same clerical job for 5 years. There she met her husband and married 4 years prior to her illness.

Two years after marriage and (6) *2 years before* her psychiatric disorder the couple *moved to Bergen County* and bought a home. They both continued to work, and kept up their friendships, social life, and cultural interests in New York City. They made little effort to socialize with neighbors or religious groups in Bergen County.



The patient's husband was loving, considerate, affectionate, and helpful around the house and yard. (7) *Neither he nor the patient had had much experience with younger children* and he gave her little assistance with the baby's care.

Therapeutic efforts included interviews with the patient individually and sessions attended by both the patient and her husband. In the first interview they came to understand their poor preparation for child rearing and suburban family life. Their main interests were in New York City. As much as they wanted a child, they both, and particularly the patient, had to sacrifice a lot for it. The patient could no longer work outside the home, see her friends, enjoy her cultural interests. She had no local substitutes, either friends or interests. She realized that loss of her mother as a young child and of her father at the age of 12 on the one hand made her more fearful of losing her baby but, on the other, left her with little conscious personal experience of the satisfactions of a parent-child relationship. She could never remember playing with dolls. The main emphasis in her childhood, especially after her father's death, was her sister's and her own working to support themselves.

Recognition of her needs and encouragement to face and solve them led to solution and action. Fortunately her mother-in-law was a loving, maternal woman who could find much time to visit her son and daughter-in-law during the day. By the second and third interviews the patient had begun to enlist the aid of her mother-in-law both as adviser and periodic baby sitter. She began to sleep well and was less fearful. Meanwhile, she investigated a local chapter of Hadassah and the possibility of courses at the local community college. She began to socialize more with her neighbors for coffee and "talk with the girls" in the mornings and she and her husband mingled with couples in the evenings.

By the fourth session she was coming for interviews every other week, by the sixth, monthly. She had taken up golf with friends, while her mother-in-law and husband baby sat, was taking an art course at the local college, and was doing publicity work with Hadassah. She and her husband were socializing regularly with their new local friends. She required a total of nine visits over a period of 7 months.

This case suggests another point. Patients who respond well have available experienced, loving, trusted, helpful friends and/or relatives to advise, guide, and help them learn the maternal role, its duties, joys, and responsibilities. Cases without response seem to be those in which no such help can be obtained. Moreover the patient had a relatively low social history number (7). Prognosis in a disorder may be in part a function of (a) numbers of environmental strains and (b) availability of practical assistance and opportunity to eliminate present-day strains. Of course these are not the only important variables—personality and constitution are also related.

These patients have not been helped completely to reorganize their personality structures, as might be accomplished with intensive psychoanalysis. They have, however, been assisted through a difficult adjustment by relatively simple procedures.

### Comment

In most of these cases the same social therapeutic principles apparently apply. These and many other psychiatric maternity patients seem to benefit from:

1. Help from women experienced in the care of infants, assistance when they are physically weak and confused, and guidance so they may learn the responsibilities and pleasures of maternity themselves. This means they need good relations with loving female friends and relatives, or substitutes.
2. Understanding, emotional support, and practical assistance from a loving husband, who himself will do well to recognize, learn about, and respect the job women do in the home. Moreover, where there is a problem, efforts should be made to assist a good sexual adjustment. Oftentimes husbands

whose work has meant being away from home for long periods, nighttime work, or study and the like, should consider organizing a program which is less strenuous for themselves and their families.

3. Leisure time—outside activities, social life with husband and friends, both to continue their pleasure in living while they learn to enjoy the maternal role, and also to provide a much needed break in the routine of "mother's never-ending day." Wives need not give up interests and satisfactions from their previous life, but merely reorganize their schedules, with the help of assistants. Everyone needs interesting new stimuli and self-expression gained by changing activities with definite rewards and pleasures.

4. Competent medical attention from a trusted physician for themselves and their babies, regular examination, as well as support in emergencies. Confidence in the doctor leads to relief of anxiety during and after pregnancy, about physical illness, and about the baby's welfare.

5. Recognition of their limitations and restriction of other responsibilities, such as sharing the care of aged relatives or avoiding when possible the assumption of special burdens, such as moving late in pregnancy or soon after delivery.

6. Discussion of their plans, fears, hopes, and problems with their husbands, relatives, doctors, and friends. This provides information and leads to planning and foresight. When they are prepared in advance to meet emergencies, they are not so easily overwhelmed and driven into a psychiatrist's office. Discussion with the husband is most profitable if it works both ways. He should share his thoughts with his wife for the same reasons. Not only does this help him, but it also gives her a greater feeling of being identified with his career, and being loved and appreciated.

The task of the physician seems to be to help the patient recognize these needs and do something about them, as well as to understand something of her underlying personality dynamics. Everyone encounters vicissitudes in the course of everyday living but persons who are more susceptible by reason of constitution or early experiences react with greater emotional disturbance. These studies indicate that several types of strains are particularly burdensome to the marginally adjusted woman during the period of childbearing. Recognition of these in advance may lead to possible prediction of later emotional difficulties and even possible prognostication of the severity of the disorder. When the environmental situation is not intolerable, however, in many cases thoughtful planning and management of these social factors may contribute to eventual alleviation with consequent psychiatric improvement after relatively few interviews.

Social factors alone are probably not producing these disorders. There are undoubtedly physiological factors as well as personality variables.<sup>7</sup> Women of certain personality types seem regularly to use poor judgment and get into difficult social situations.<sup>9</sup> Thus a spiraling process is possible. Unstable women may involve themselves with social strains and thus perpetuate their personality difficulties. If they push themselves too far and too fast an emotional disorder is precipitated, often at the period of childbearing.

Social strains amenable to improvement apparently play a larger part in the development of many emotional illnesses of maternity patients than in the disorders of other comparable young married women. These illnesses seem to respond better to improvements in the environment. This is not surprising. An emotional disorder which develops as a result of an acute social event, such as pregnancy and childbearing in a woman's life, should reasonably be expected to respond to social readjustments more readily than a disorder which has developed in the nonchildbearing period and which is related to more

chronic personal and emotional problems. Since psychotherapy which emphasizes these social factors apparently is more successful with many psychiatric maternity patients we may conclude that social problems have some causal relationship in many of these cases.

Social forces also may play a part, but to a lesser degree, in some of the psychiatric disorders of nonchildbearing women. Some of these women also responded quickly to socially oriented dynamic psychotherapy. When the patient's problems are in large part environmental she is daily being subjected to painful emotionally traumatizing experiences. Her ability to respond to purely insight psychotherapy under these conditions is lessened. Once she understands and can begin to alleviate some of the present-day strains her response to insight psychotherapy may proceed more rapidly.

Helping new mothers manage their environmental strains will not likely prevent every emotional disorder of pregnancy. Patients whose difficulties are more deep seated and are related to constitutional factors or experiences of early childhood, or who are unable to improve their social situations readily, require many more psychotherapeutic sessions and their prognosis is poorer. Those with bad present-day situations must learn to live with regularly recurring painful experiences. These patients require more intensive analytical insight-gaining therapy. They need a reorganizing of attitudes and values to permit adjustment despite a chronically unpleasant situation. Both types of problems have a poorer prognosis and require specialized attention.

An experiment is in progress to use this growing knowledge to assist in the social and psychological preparation of mothers for maternity. If these experiments should prove fruitful such efforts may be useful with others at other periods of life. Better educational preparation for the demands of a new role in life may help prevent or diminish emotional difficulties even in the marginally adjusted.

Meanwhile obstetricians and general practitioners may have considerable success in the management of the emotional aspect of many maternity patients both before and after the development of psychiatric symptoms. Since in most cases it seems that social factors have considerable importance, efforts at pointing out the pleasures and satisfactions and at diminishing the social stresses and strains may effect considerable benefit and may help prevent more serious emotional difficulties.

### Summary and Conclusions

1. Two separate studies were performed related to the hypothesis that social and environmental factors have considerable importance in the emotional disorders of pregnancy and childbearing. In the first, on the basis of patients' responses to a questionnaire, an attempt was made to predict their later emotional reaction during 4 months after delivery. In the second, two methods of psychotherapy were compared in an experimental and a control group, one using dynamic therapy alone, the other with greater attention to the amelioration of social strains.

2. A relatively high percentage, 30 per cent, of normal women showed some degree of emotional upset after delivery of a normal child. This may be related to the type of stressful living found in a rapidly growing suburb.

3. The social history prediction study was quite successful at a very high level of statistical significance. Higher prediction scores were generally associated with greater emotional disturbance. Psychiatric maternity patients had higher scores as a group, the most severely ill psychiatric maternity patients had the highest scores.



4. The therapy study was also successful and statistical calculations indicate that the results were quite significant. A psychotherapeutic approach in which the therapist worked not only with the patient's personal psychodynamics but also pointed out social strains and recommended their improvement was more effective in married women patients generally but was particularly so in the maternity group when compared to a control group of nonmaternity psychiatric married women patients.

Psychiatric maternity patients subjectively did better, required fewer sessions, continued treatment more often after an initial consultation, and required less hospital care when social strains were alleviated along with their insight therapy.

5. Prediction scores and possibility of environmental improvement seemed highly related to prognosis.

6. A typical case history with its management was presented. The social factors that relate to a woman's adjustment to the experience of maternity were discussed.

7. Suggestions were presented to the obstetrician and the general practitioner for recognizing potentially ill women from their background histories. The important social readjustments were outlined that the physician may recommend to his patient with the hope of, first, preventing or minimizing some disorders and, second, more readily assisting the patients who already have developed emotional complications of pregnancy. Such an approach may not work such profound personality changes in patients as are accomplished by intensive psychoanalysis, but many potential psychiatric patients may be helped through a very stressful adjustment period.

8. An experiment has been begun of introduction of this social information into antenatal classes with the hypothesis that such an educational procedure may serve a preventive function.

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## OBSERVATIONS ON "PATHOLOGIC" FETAL BRADYCARDIA\*

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SINCE 1893 when Von Winckel<sup>1</sup> drew attention to the association of fetal bradycardia with poor fetal outcome, slowing of the fetal heart rate to less than 100 beats per minute between contractions has been considered the chief criterion of fetal distress.<sup>2</sup> Application of this dictum to clinical obstetrics has produced a number of seeming inconsistencies, for bradycardia of this magnitude has been frequently noted both in the antepartum period and during labor, yet the infant has been in good condition at birth.

In preliminary reports of the electronic evaluation of the fetal heart rate by continuous recording,<sup>3, 4</sup> an attempt was made to differentiate "physiologic" and "pathologic" bradycardia by their respective "V" and "U" shaped patterns.

The "pathologic" fetal bradycardia which was discussed in detail in these earlier studies was shown to be due to umbilical cord compression.<sup>4</sup> In this report a different type of "pathologic" fetal bradycardia will be described which is thought to be due primarily to acute fetal hypoxia. A hypothesis will be advanced which may explain the underlying mechanism. However, the need to measure continuously and quantitatively the many factors which may influence the fetal heart rate precludes definite conclusions at this time.

### Patients and Procedures

The tracings discussed in this study were recorded from 7 patients and selected from some 500 fetal electrocardiogram tracings made over the past 3 years using techniques previously described.<sup>3-5</sup> The patterns discussed here are graphs of the instantaneous fetal heart rate and have been selected to demonstrate the association of a particular type of fetal bradycardia with a certain clinical situation. It is not definitely known, however, whether a cause-and-effect relationship exists.

The infant's condition was scored by the Apgar<sup>6</sup> rating. In 4 patients (Nos. 57-051, 56-0908, 58-226, 58-229) uterine contractions were determined by abdominal palpation and checked against increased baseline activity on the fetal ECG record. Although this method produces some error in timing, this is minimal. In the remaining 3 patients (Nos. 58-212, 58-130, 58-138), the frequency and amplitude of the contractions were determined with an intra-amniotic catheter attached to a strain gauge and associated recording apparatus so that the amniotic fluid pressures were recorded continuously.

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### Observations

**Physiologic Bradycardia.**—The transitory V-shaped bradycardia associated with uterine contractions and increased intracranial pressure has a different pattern from U-shaped pathologic bradycardia.<sup>3, 4</sup> Fig. 1 is the fetal heart rate pattern noted during a contraction in a primigravid patient at 4 cm. dilatation. About 20 seconds after the onset of the contraction, there is an abrupt drop in heart rate to about 80 beats per minute for about 7 to 8 seconds, then the heart rate returns to normal about 20 seconds before the contraction is over.

**Bradycardia Associated With Umbilical Cord Compression.**—The temporal relationship between the onset of the contraction and the beginning of a particular type of pathologic bradycardia appears to be of significance. If umbilical cord compression is associated with a contraction, slowing of the fetal heart begins 10 to 15 seconds after the contraction begins. If the contraction, and hence the compression, is short lived and mild, the fetal heart rate returns to precompression levels almost immediately when the cord is released.<sup>4</sup>

Fig. 2, A is the heart rate pattern, during early labor, of a fetus who was presenting as a double footling breech and whose umbilical cord was later shown to have prolapsed between its thighs. The bradycardia noted here was probably related to cord compression during the uterine contraction. In this, and the associated figures (Fig. 2, B and C), bradycardia is indicated by an unbroken line whenever the fetal heart rate is less than 100 beats per minute. The broken line indicates the time the fetal heart rate takes to return to normal following this bradycardia.

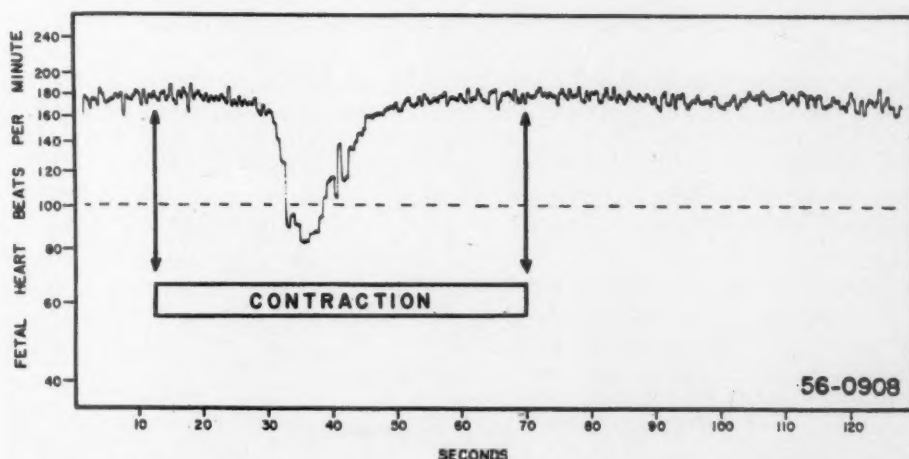


Fig. 1.—Physiologic bradycardia recorded from a fetus during a uterine contraction at 4 cm. dilatation in a primigravid patient. Note transitory bradycardia in the middle of the contraction.

With more prolonged cord compression, such as may be present during the longer and more forceful contractions of late labor (same patient), a longer period elapses after the end of the contraction before the fetal heart rate returns to normal (Fig. 2, B).

A comparison of the physiologic bradycardia of Fig. 1 with the pathologic bradycardias of Fig. 2, A and B shows the former to have an abrupt drop in fetal heart rate to 100 beats per minute, then an 8 second period of bradycardia and rapid return to normal 20 seconds before the contraction is over. In the latter instances, the bradycardia begins earlier, the fall is more gradual, it lasts

longer, and is more profound. The return to normal is delayed beyond the end of the contraction especially in Fig. 2, *B* where the contraction and presumably the cord compression were longer than in Fig. 2, *A*.

While the mechanism of this type of bradycardia is not known, there are certain observations which suggest that the physiologic changes producing the bradycardia associated with momentary compression of the cord may be different from those present in prolonged cord compression. In the first instance (Fig. 2, *A*), the rapid drop in fetal heart rate with cord compression and the rapid return to normal immediately following release suggest mechanisms other than hypoxic myocardial depression since this response to change in oxygen concentration would probably be more gradual. It seems unlikely that this would take place in the 10 to 15 seconds immediately following the insult.

Observations of fetal lambs during experimental compression of the umbilical cord suggest that the initial portion of bradycardia may be due to vascular reflexes following the effect of momentary acute hypoxia on the vagus center and pressure changes in the umbilical arteries and veins and larger fetal vessels.<sup>7, 8</sup>

With prolonged compression of the umbilical cord the fetal heart rate does not return to normal immediately after the pressure is released (Fig. 2, *B*) even though the normal fetal hemodynamics may have been re-established. This delayed bradycardia may be related to hypoxia resulting from continued interference with the fetal oxygen supply which inevitably follows if the cord is compressed for a sufficient time.

*Bradycardia Associated With Frequent and Strong Contractions.*—In contradistinction to the bradycardia associated with cord compression (Fig. 2, *A* and *B*), the bradycardia noted with frequent and very strong uterine contractions does not begin immediately after the onset of the contraction but after a consistent delay of 25 to 30 seconds (Fig. 2, *C*) and does not fall to less than 100 beats per minute until 50 seconds after the beginning of the contraction. The delayed onset of bradycardia and its gradual alleviation in the interval between contractions suggest the possibility that this type of bradycardia is primarily due to hypoxia.

It has been observed that fetal lambs and guinea pigs which are slowly (over a period of minutes) rendered hypoxic, usually respond first with tachycardia followed by bradycardia; if they are made acutely (within seconds) hypoxic the initial response is bradycardia.<sup>7, 9-11</sup> Whether or not these observations are applicable to the human fetus is not known.

### Possible Working Hypothesis

The physiologic mechanism underlying this type of hypoxic bradycardia has been suspected but not definitely clarified. It is possible that the frequency and amplitude of the uterine contractions interfere with the inflow and outflow of blood to and from the intervillous space in such a manner that the oxygen available for the fetus is depleted. Such an idea is not new and has been proposed in one form or another for many years.<sup>12-19</sup>

Fig. 3 is a schematic diagram of a detailed version of a similar hypothesis and is based on the idea that the volume of blood flow into the intervillous space is dependent largely on (a) the maternal arterial inflow which is related to the systemic blood pressure and caliber of the arterioles, (b) the venous outflow, and (c) the intramyometrial pressure which at the onset of a contraction first cuts off the venous outflow and, with increased amplitude, finally cuts off arterial inflow, thereby physiologically isolating the intervillous space.



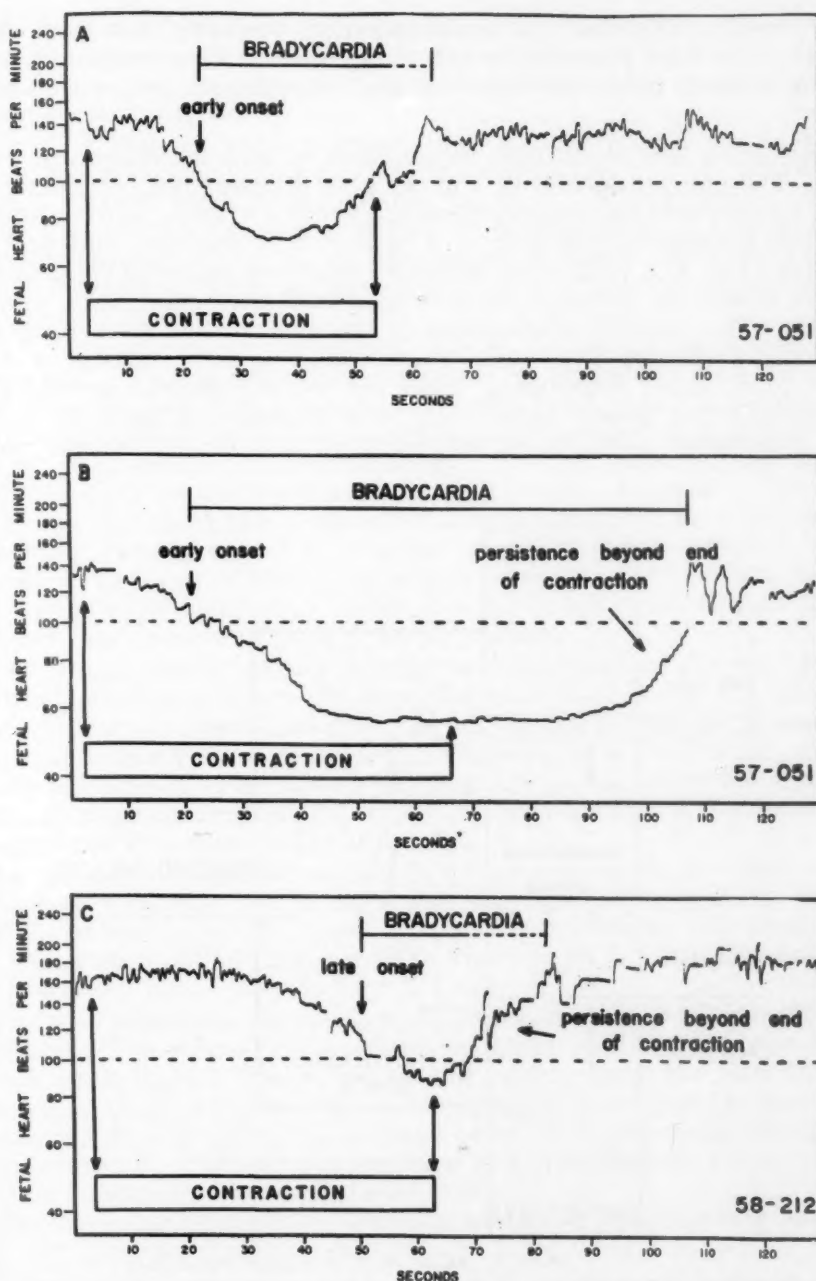


Fig. 2.—A, Bradycardia associated with a uterine contraction (early labor) noted in a fetus who was presenting as a double footling breech and who had the umbilical cord prolapsed between the thighs. The fetal heart rate slows almost immediately and is less than 100 beats per minute about 15 seconds after the onset of the contraction and returns to normal shortly after the contraction finishes.

B, Prolonged and profound fetal bradycardia noted in the same patient as Fig. 2, A as a result of a longer uterine contraction (late labor). About 40 seconds elapse after the contraction is over before the fetal heart rate returns to normal. (Frequency and duration of contractions in Fig. 2, A and B were determined by abdominal palpation and correlated with increased electrical activity of the base line of the fetal ECG tracing.)

C, Fetal bradycardia associated with frequent and strong uterine contractions. Note the 50 second delay after the onset of the contraction before the fetal heart rate is less than 100 beats per minute and compare this interval with the corresponding intervals of Fig. 2, A and B. Note also the persistence of bradycardia after the contraction is over. (Amplitude and frequency of contractions determined from amniotic fluid pressure tracings.)

With intact membranes, the intramyometrial pressure rises more sharply than the amniotic fluid pressure so that at the acme of a contraction it may be two to three times as great, and therefore high enough to interfere with uterine blood flow.<sup>16</sup>

The dynamics and physiologic implications of such a system will now be discussed. The upper drawings of Fig. 4, *A* to *E* schematically illustrate vascular and intramyometrial changes present during a uterine contraction. The amniotic fluid pressure curves (Fig. 4, *A* to *E*, middle tracings) and fetal heart rate patterns (Fig. 4, *A* to *E*, lower tracings) have been recorded from an actual patient and, except for minor errors associated with photography and graphing, are accurate. The dynamic relationships of the myometrium, intervillous space, and chorionic villus are presented schematically to make discussion clearer (Fig. 4, *A* to *E*, upper drawings). Since the intramyometrial pressures were not determined in the patient under study, this discussion is based on Caldeyro-Barcia's<sup>16</sup> observation that the intramyometrial pressure is two and one-half

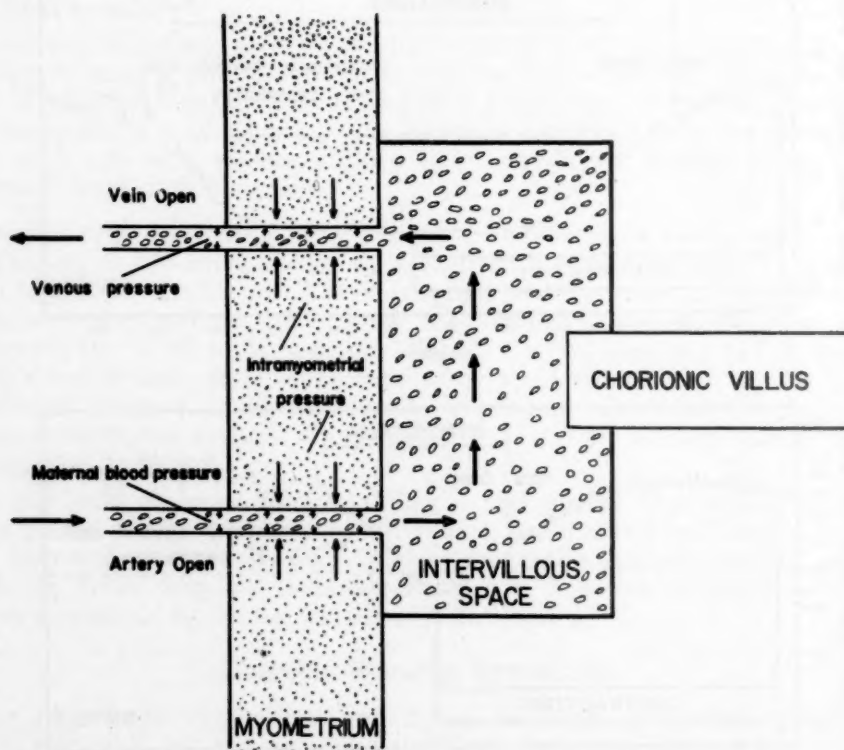


Fig. 3.—Schematic representation of the hemodynamics governing oxygenation of the intervillous space. The intramyometrial pressure tends to interfere with the arterial inflow and venous outflow by compression of the vessels. The degree of interference is directly related to the pressure differential existing between the systemic blood pressure of the mother and the intramyometrial pressure.

to three times the amniotic fluid pressure. Hence, if the amniotic fluid pressure is 50 mm. Hg at the acme of a contraction, the intramyometrial is between 125 and 150 mm. Hg.

The fetal heart rate pattern associated with the relaxation and contraction phases of a single uterine contraction will be presented serially so that the hemodynamic changes in the intervillous space, the intramyometrial pressure changes, and the fetal heart rate patterns can be correlated simultaneously. Each of the

amniotic fluid and fetal heart rate graphs of Fig. 4 shows progressive development of the curves. Correlation with the schematic diagrams is aided by a horizontal line with accompanying markers indicating the particular phase of the graphs being charted.

Fig. 4, *A* shows a portion (heavy lined section of amniotic fluid pressure curve) of the relaxation phase of a uterine contraction and the associated fetal heart rate pattern which is immediately below it. The uppermost illustration indicates that the myometrium is relaxed (light stippling) so that both arterial and venous channels are open, thereby permitting free inflow to, and outflow from, the intervillous space so that no congestion is present (moderate number of red blood cells).

At the beginning of a contraction (Fig. 4, *B*) the venous outflow is at first not impaired. As the contraction increases in amplitude and the intramyometrial pressure rises, it is completely occluded (vein closed in schematic drawing). The arterial inflow is still maintained since the intramyometrial pressure is not yet great enough to close the artery. The net result is congestion of the intervillous space (more red blood cells in schematic diagram). The chorionic villus is now immersed in a relatively stagnant blood pool from which the oxygen is being rapidly removed. As the oxygen pressure gradient across the chorionic villus becomes lower, the oxygen saturation of the fetal hemoglobin falls. In the early contraction phase this fall is not great enough to produce fetal heart rate changes (Fig. 4, *B*, lower tracing).

As the contraction becomes stronger and approaches its acme (Fig. 3, *C*), the intramyometrial pressure becomes great enough (heaviest stippling of myometrium in the schematic drawing) to cut off completely the arterial inflow, thereby producing total stagnation of the intervillous space blood and physiologically isolating it from further oxygenation by the maternal blood stream. The net effect is an accentuation of the congestion (Fig. 4, *B*) until the fetal heart responds by a mild bradycardia (Fig. 4, *C*).

As the uterine contraction enters the relaxation phase (Fig. 4, *D*), the arterial lumen becomes patent again but very little, if any, oxygenated blood enters the intervillous space since the venous outflow is still occluded. The fetus, therefore, is still hypoxic and the bradycardia is not relieved (Fig. 4, *D*, lower graph).

Fig. 4, *E* illustrates the relaxation phase immediately following the uterine contraction. The relaxed myometrium no longer occludes the venous outflow and once again there is free inflow to, and outflow from, the intervillous space. The stagnant blood is replaced by well-oxygenated blood and the normal oxygen pressure gradient is gradually re-established, thus increasing the percentage oxygen saturation of the fetal hemoglobin with a consequent return of the fetal heart rate to normal (Fig. 4, *E*, lower tracing).

The foregoing hypothesis is based primarily on the following assumptions:

1. Acute fetal hypoxia produces bradycardia.
2. The intervillous space has a measurable oxygen reserve.
3. The oxygen saturation of intervillous space blood is directly dependent on the rate of flow through the intervillous space (assuming adequate maternal oxygenation).
4. The differential between the intramyometrial pressure and maternal blood pressure has a profound effect on the rate of flow through the intervillous space.
5. Re-establishment of normal intervillous space oxygen reserve is dependent largely on adequate relaxation time between contractions.

This hypothesis can be tested further by studying (a) normotensive patients in whom there is increased amplitude and frequency of uterine contractions so that, first, there would be a greater than normal differential pressure

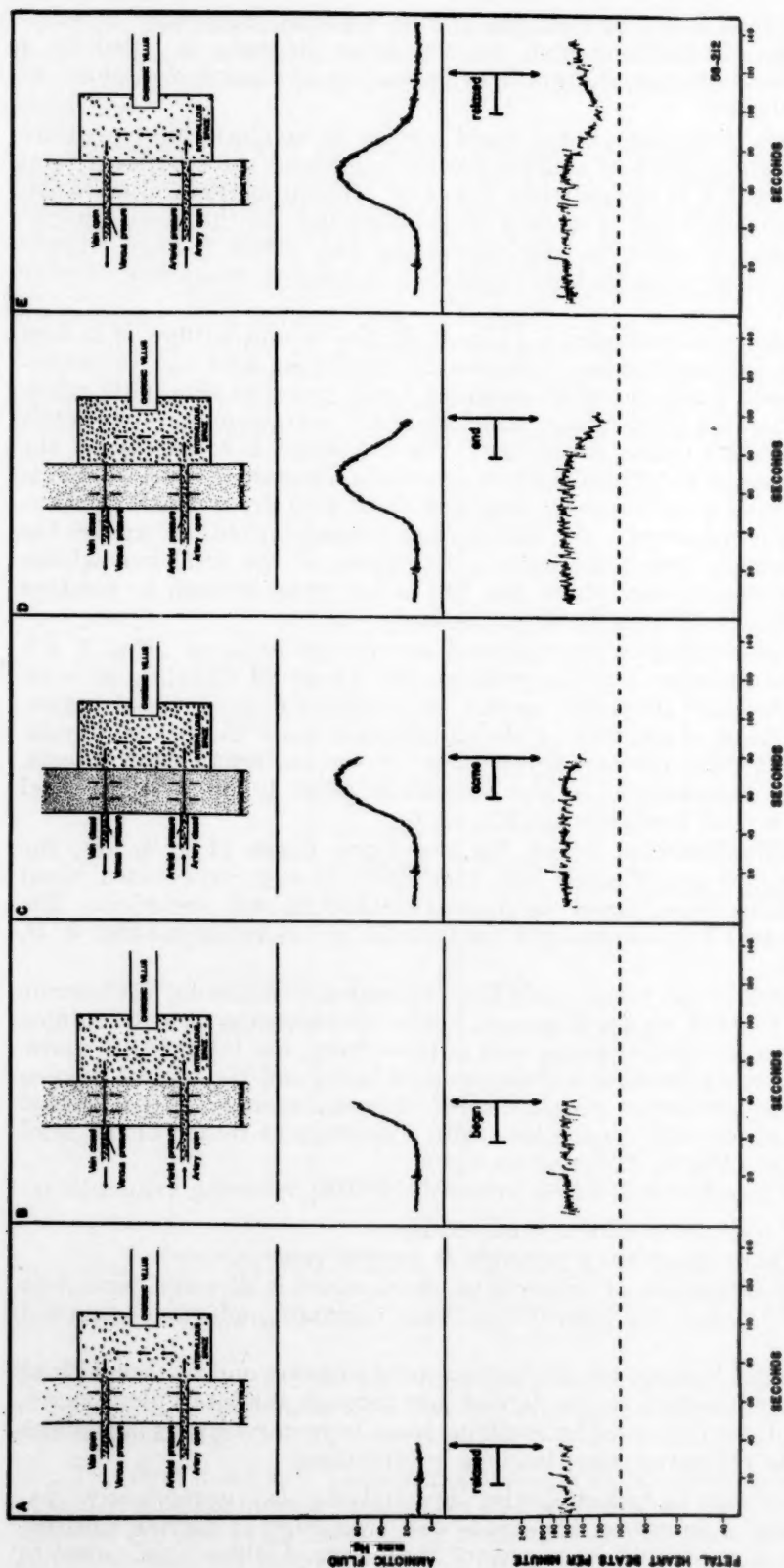


Fig. 4.—The progressive amniotic fluid pressure changes in the relaxation and contraction phase of a single uterine contraction (middle tracings) are correlated with associated fetal heart rate changes (lower tracings) and the altered hemodynamics which are present at that time (upper drawings).

The horizontal line and accompanying markers lying between the lower drawings indicate the phase of the contraction at that time. The increase in intramyometrial pressure (2.5 to 3 times the amniotic fluid pressure) is indicated by heavier stippling of the myometrium and the degree of congestion by the number of red blood cells in the intervillous space (upper drawings).

- A, Relaxation phase; Intramyometrial pressure minimal, vein and artery open, free blood flow through the intervillous space.
- B, Beginning of contraction phase; Intramyometrial pressure rising, vein closed, artery open, some congestion of intervillous space.
- C, Acme of contraction; Intramyometrial pressure maximum, both vein and artery closed, stagnation of intervillous space.
- D, End of contraction phase; Intramyometrial pressure decreasing, vein closed, artery open, stagnation of intervillous space.
- E, Relaxation phase; Intramyometrial pressure minimal, vein and artery open, free blood flow through the intervillous space.



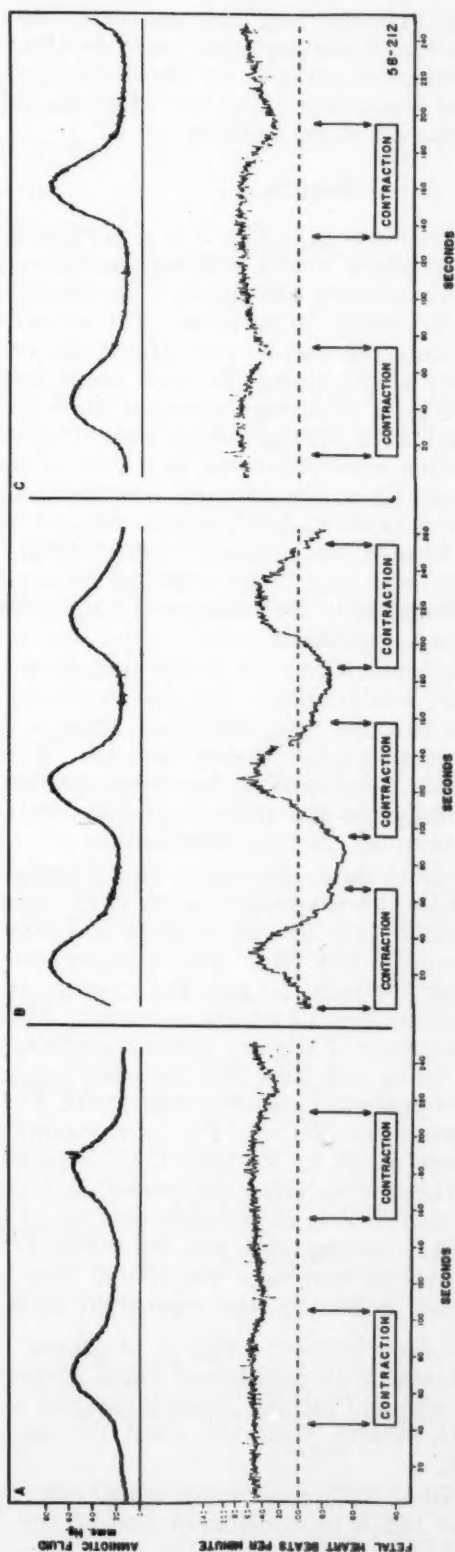


Fig. 5.—The effect of increased frequency and amplitude of uterine contractions on the fetal heart rate. The duration of the contractions is given by the labeled rectangles under the fetal heart rate pattern; the actual pressures involved can be determined from the associated amniotic fluid pressure tracing.

A, Mild fetal bradycardia associated with contractions occurring at a rate of about five every 10 minutes.

B, Accentuation of fetal bradycardia when the contractions are more frequent and of greater amplitude.

C, Lessening of fetal bradycardia as the contractions become less frequent and weaker. Note the greater degree of bradycardia with the second contraction which is stronger.

between the intramyometrial pressure and the maternal blood pressure and, second, the relaxation time between contractions would be shortened, producing fetal bradycardia; (b) hypotensive patients in whom the uterine contractions are of average amplitude and frequency. The net effect should be the same as given in (a) and fetal bradycardia should follow.

### Results

*The Effect of Uterine Contractions.*—Fig. 5 is a portion of the fetal heart rate pattern noted in a patient whose uterus was very sensitive to Pitocin. Fig. 5, A shows the fetal heart rate pattern associated with uterine contractions occurring at the rate of about five every 10 minutes. The amniotic fluid pressure between contractions was 10 mm. Hg and 60 mm. Hg at the acme of a contraction (upper tracing). A very slight change in fetal heart rate is seen toward the end of the contraction. Fig. 5, B demonstrates the more profound and prolonged bradycardia associated with stronger and more frequent contractions. In this instance the contractions were occurring at a rate of about seven every 10 minutes and reached 80 mm. Hg at the acme of a contraction (upper tracing, Fig. 5, B). This momentary episode of bradycardia was not apparently detrimental to the fetus. As the Pitocin was gradually metabolized, the contractions became less frequent and the fetal heart rate returned to normal (Fig. 5, C). This graded fetal heart rate response to frequency and amplitude of contractions appears to support the proposed hypothesis.

Clinically, it is also well known that too rapid induction of labor may be associated with profound fetal bradycardia. The instantaneous fetal heart rate pattern in this circumstance has not been described since it is difficult to determine this accurately with present auscultatory methods. With the continuous recording techniques previously developed<sup>5</sup> it has been possible to confirm this clinical observation and actually see the pattern of fetal bradycardia and irregularity associated with "tetanic" uterine contractions.

In the limited observations to date, the degree and duration of bradycardia appear to be influenced more by the frequency rather than the amplitude of the individual contractions provided they are of average intensity, i.e., maximum amniotic fluid pressure of about 50 mm. Hg. Fig. 6 illustrates this point. The upper tracing shows strong contractions (60 mm. Hg at acme, 10 mm. Hg tonus) occurring at the rate of about six per 10 minute interval. Mild bradycardia is noted. Fig. 6, B shows contractions of slightly greater amplitude now occurring more often and with higher tonus (20 mm. Hg) between contractions. In this instance, bradycardia is more profound and prolonged. In Fig. 6, C, while the amniotic fluid pressure is lower (45 to 50 mm. Hg) at the acme of a contraction, the tonus between contractions is 25 to 35 mm. Hg. Marked bradycardia is present even though the uterine contractions are weaker and less frequent than the other 2 cases shown in Fig. 6. This is probably due to the abnormally high amniotic fluid pressure between contractions and the myometrial hypertonicity which is great enough to interfere seriously with blood flow to and from the intervillous space during what is usually the relaxation phase of the uterus.

*The Effect of Maternal Hypotension.*—Fig. 7, A shows profound bradycardia and irregularity associated with a maternal blood pressure of 80/40 mm. Hg recorded from a patient who had fainted about 2 minutes earlier. For comparison, the fetal heart rate pattern recorded when the patient was normotensive is shown in Fig. 7, B.

With hypotension associated with conduction anesthesia, fetal bradycardia is also seen. Clinically, this has been considered one of the hazards of such anesthesia<sup>20</sup> but the actual bradycardia pattern has not been described. Fig.

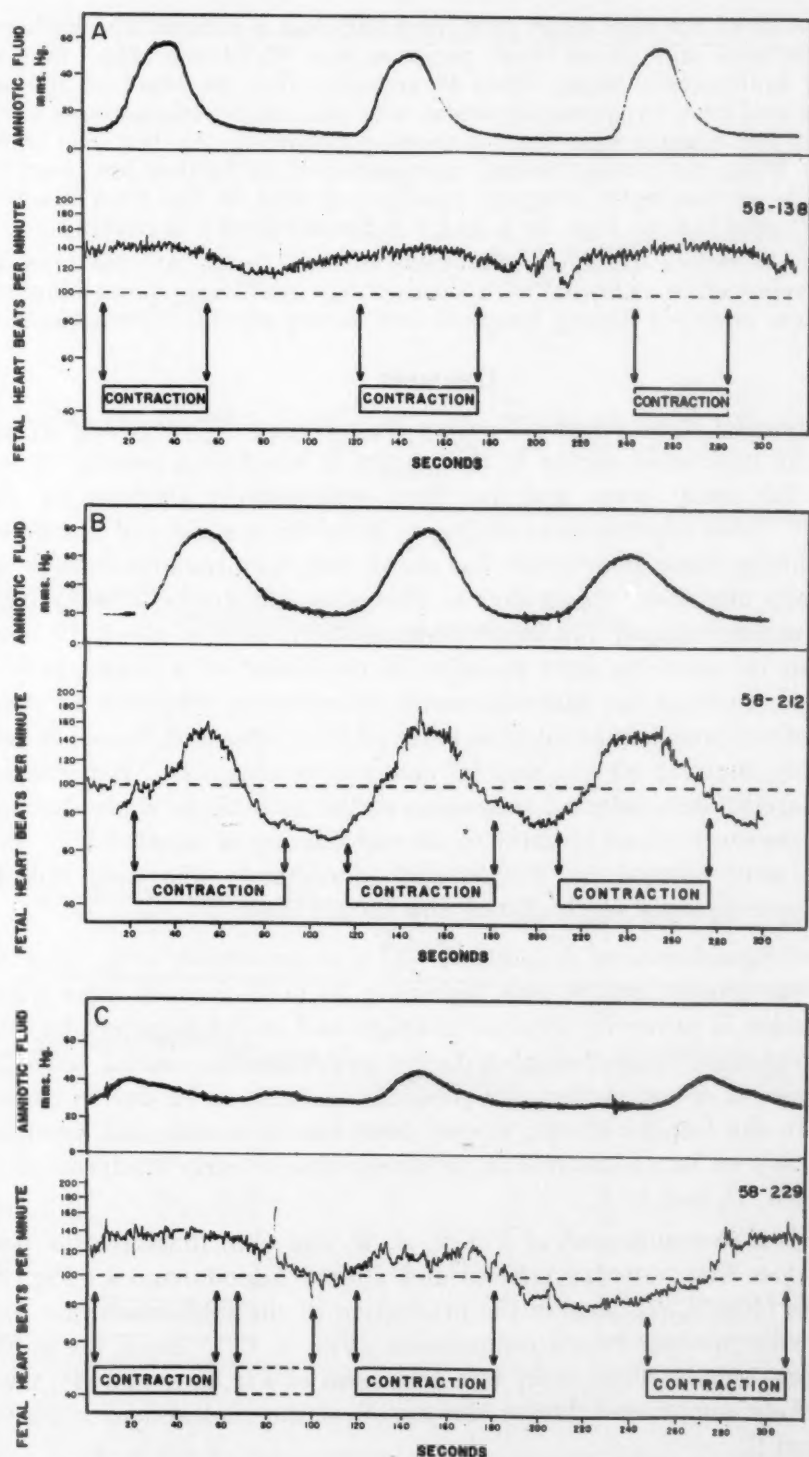


Fig. 6.—The relationship between fetal bradycardia and increased frequency of uterine contractions and increased uterine tone. The contractions associated with Fig. 6, B are more frequent and of higher amplitude than those noted in Fig. 6, A. The tonus between contractions is also higher. Fig. 6, C shows the profound bradycardia associated with increased uterine tone; however, the actual contractions are of less than average intensity.

7, *C* is a graph of the fetal heart rate recorded from a patient who had received caudal anesthesia and whose blood pressure was 90/70 mm. Hg. The slowly developing bradycardia began 30 to 40 seconds after the onset of the uterine contraction and grew progressively worse with succeeding contractions and went to 80 beats per minute with the contraction following the last one shown in Fig. 7, *C*. When the patient became normotensive, no further bradycardia was noted. It is interesting to compare the development of the fetal bradycardia of Fig. 7, *C* with that of Figs. 5, *A* and *C*. The similarity is striking.

A more extensive study (unpublished) of fetal heart rate patterns during maternal hypotensive episodes with conduction anesthesia shows similar patterns to those recorded during frequent and strong uterine contractions.

### Comment

*Experimental Basis for the Working Hypothesis.*—The working hypothesis schematically illustrated earlier in this report is based on a concept which has been held for many years and has been progressively clarified by various workers.<sup>12-19</sup> With continuous recording of intervillous space and amniotic fluid pressures during labor Hendricks<sup>19</sup> has shown that the pressures in these spaces are essentially identical. Eastman,<sup>19</sup> in discussing Hendricks' report, indicated that Prystowsky<sup>18</sup> found the intervillous space pressures about 10 mm. Hg greater than the amniotic fluid pressure at the height of a contraction. The myometrium overlying the placenta would therefore be subjected to the same intramyometrial pressures as the remainder of the uterus and, hence, be capable of completely shutting off the arterial and venous channels. Experimentally, Caldeyro-Barcia<sup>16</sup> demonstrated congestion of the intervillous space during prolonged uterine contractions by delay in the mobilization of injected I<sup>131</sup>. Similar conclusions were reached by Wright and co-workers<sup>15</sup> who used radioactive sodium chloride to study uterine blood flow during labor.

*Clinical Significance of Hypothesis.*—If this hypothesis (Fig. 4, *A* to *E*) is tenable, the type of bradycardia beginning 30 to 40 seconds after the onset of a contraction is primarily hypoxic in origin and would therefore be of more serious import than that of similar degree and duration noticed immediately after the onset of a contraction and presently thought to be due to cord compression. In the latter instance, altered fetal hemodynamics and vascular reflexes may play an important role in the production of early bradycardia (compare Fig. 2, *A*, *B*, and *C*).

Fig. 8 is a rearrangement of Fig. 2, *A*, *B*, and *C* to illustrate the possible respective roles that vascular reflexes and altered hemodynamics (Fig. 8, *A*) and hypoxia (Fig. 8, *B*) play in the production of the fetal heart rate pattern associated with prolonged cord compression (Fig. 8, *C*). Since the cord had prolapsed between the fetal thighs (see discussion of Fig. 2, *A* and *B*), the cord was most likely compressed during the period of the contractions indicated in Fig. 8, *A* and *C*.

It is probable that the prolonged cord compression (as a result of a sustained uterine contraction) shown in Fig. 8, *C*, not only altered the fetal hemodynamics but also produced a certain amount of hypoxia which triggered vascular reflexes and slightly depressed the myocardium. It is possible, therefore, that the



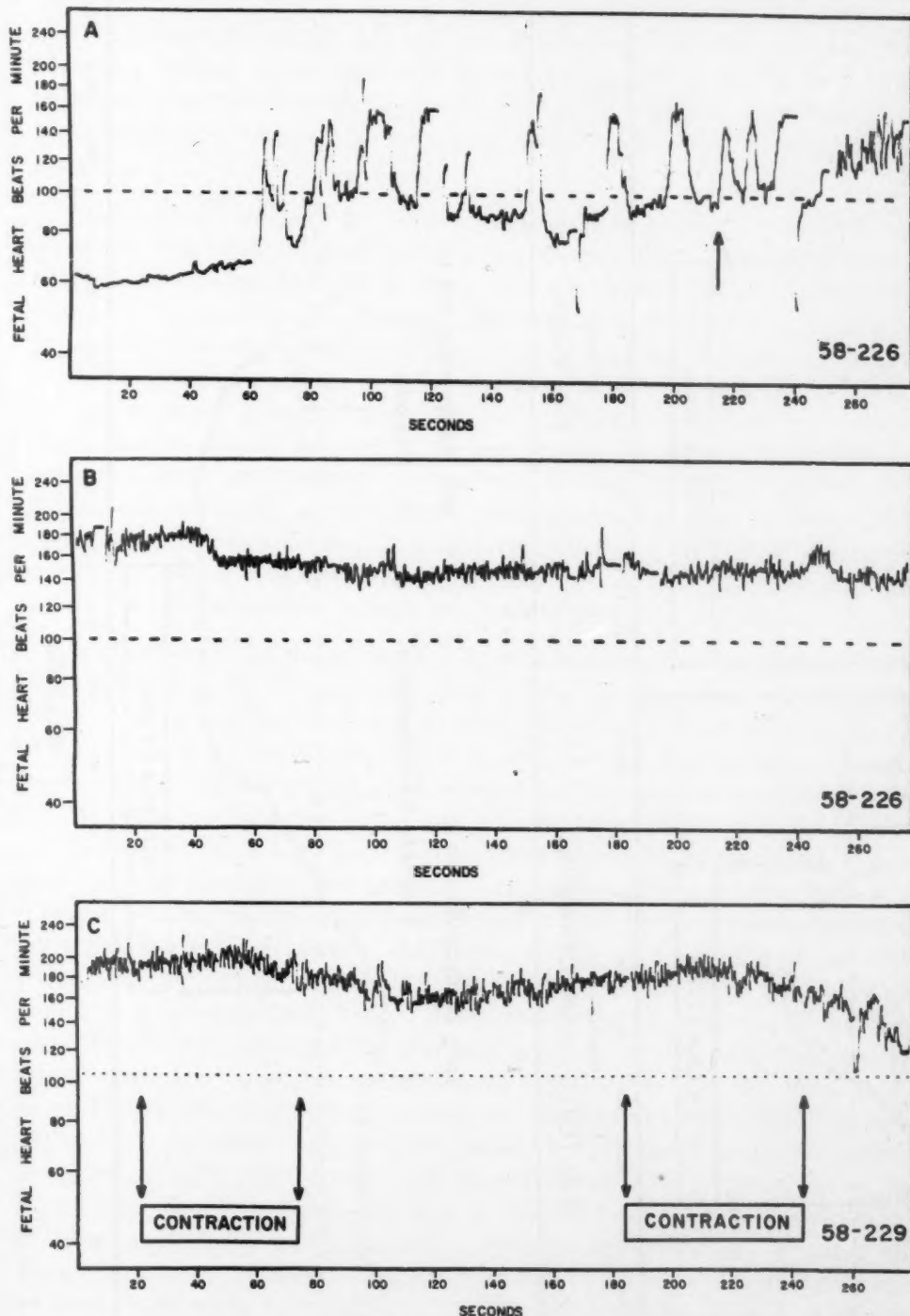


Fig. 7.—A, Profound fetal bradycardia and irregularity associated with hypotension in a patient who fainted about 2 minutes before the tracing was started. Blood pressure at the start of recording was 80/40 mm. Hg and 100/70 mm. Hg at the arrow.

B, Normal heart rate which was recorded when the patient was normotensive.

C, Slowly developing fetal bradycardia beginning about 30 to 40 seconds after the onset of uterine contractions. The patient had received a caudal anesthetic and the blood pressure was 90/70 mm. Hg. The fetal heart rate fell to about 80 beats per minute with the contraction following the last one shown and returned to normal when the patient became normotensive.

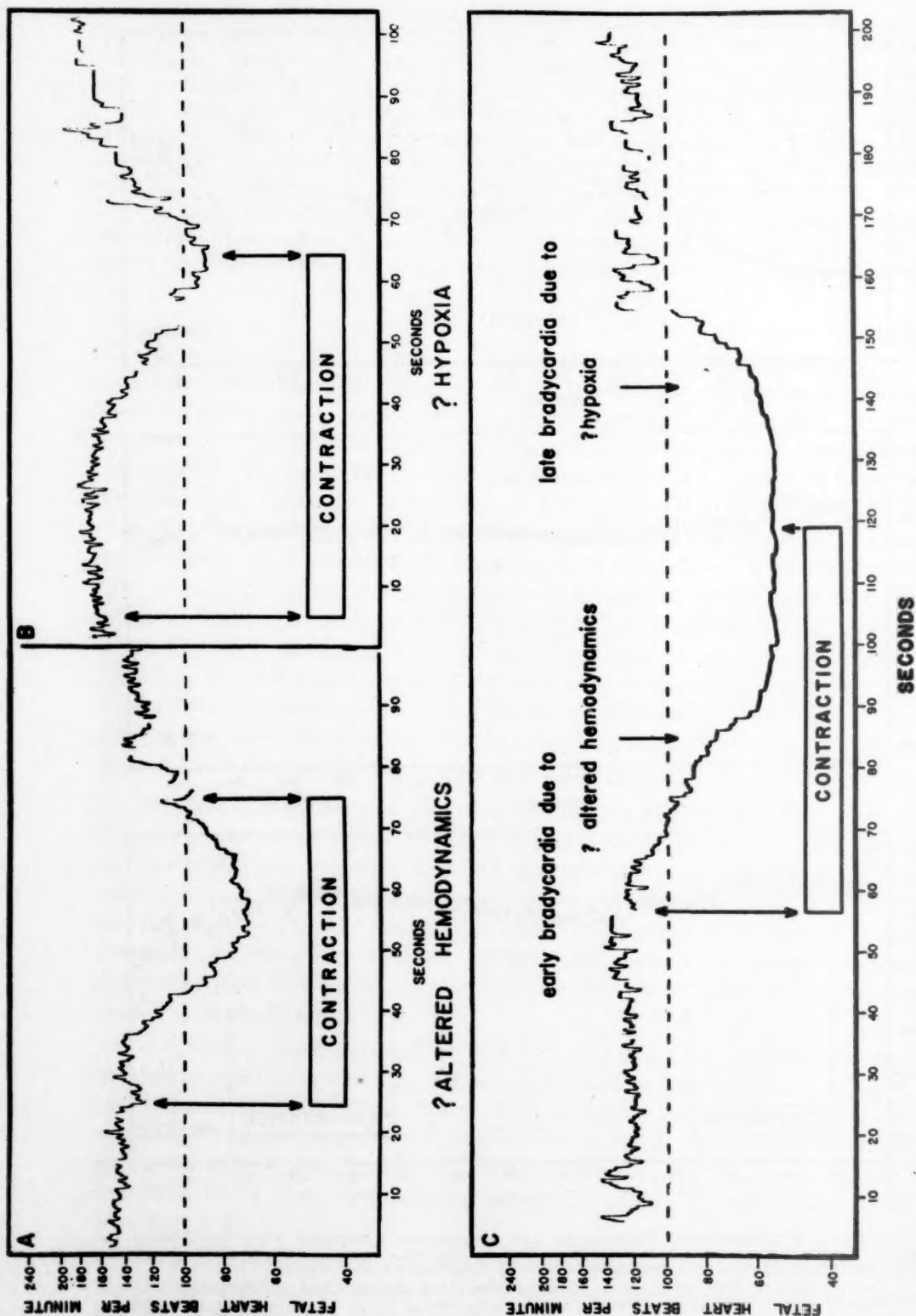


Fig. 8.—A, Transitory bradycardia associated with a uterine contraction and probable short-lived compression of a prolapsed umbilical cord. This bradycardia is thought to be due primarily to vascular reflexes and altered fetal hemodynamics. B, Transitory bradycardia associated with strong and frequent uterine contractions and thought to be primarily hypoxic in origin (see Fig. 2, A, B, and C). C, Prolonged and profound bradycardia associated with a longer uterine contraction and more prolonged compression of the umbilical cord (same patient as in Fig. 8, A). In addition to the bradycardia probably due to vascular reflexes and altered fetal hemodynamics (Fig. 8, A), a hypoxic component (Fig. 8, B) is probably present.

early bradycardia of this tracing is due primarily to altered vascular reflexes and fetal hemodynamics, and the late bradycardia due primarily to hypoxia. This idea appears to be supported by studies on lambs<sup>7</sup> and by the clinical observation that if fetal bradycardia gradually worsens and finally persists throughout the interval between contractions the fetus is frequently compromised.

*Clinical Significance of Fetal Bradycardia.*—While the small number of observed cases does not permit an extensive discussion of the significance of the patterns of bradycardia noted, there appears to be a definite relationship between the type of bradycardia and the condition of the baby at birth. With present methods of evaluation of the newborn, only a gross measurement of neonatal condition is available and the significance of subtle changes in fetal heart rate must therefore await better neonatal evaluation. At present, if the bradycardia begins toward the end of the contraction, it appears to be more serious than the bradycardia which is confined to the contraction period. Present studies (unpublished) suggest that if the pathologic U-shaped pattern of bradycardia<sup>4</sup> is progressively widening and the return to normal is associated with irregularity, this is evidence that the condition of the fetus is slowly growing worse. At delivery these infants are usually in poor condition.

*Pathologic Fetal Bradycardia.*—In previous reports<sup>3, 4</sup> an attempt was made to define "physiologic" and "pathologic" fetal bradycardia. Physiologic bradycardia was thought to be related to changes in fetal intracranial pressure as the result of pressure on the fetal skull during uterine contractions. Apart from some transitory bradycardias of short duration<sup>4</sup> the remaining fetal bradycardias by exclusion fell into the pathologic classification. While this may be correct and acceptable from a theoretical standpoint, clinically, the majority of so-called pathologic bradycardias are associated with apparently normal infants at birth. There is a need, therefore, to distinguish between the infrequent, transitory, or mild pathologic bradycardias, which may merely be a warning of possible difficulty, and the type of pathologic bradycardia (persistent and prolonged) which indicates a compromised fetus. Since the U-shaped patterns of bradycardia associated with mild umbilical cord compression, or seen with moderately frequent uterine contractions or with mild hypotension, are not associated with poor fetal condition at birth, they may be classified more reasonably as marginal rather than pathologic and thereby connote a warning of probable, rather than actual, fetal difficulty. Until long-term follow-up studies are made of infants with known fetal heart rate patterns, it will not be possible to draw sharp lines between physiologic, marginal, and pathologic bradycardias. From a clinical standpoint the rough guide set down earlier in this section ("clinical significance of fetal bradycardia") appears to be of value in the handling of a specific patient.

*Fetal Tachycardia.*—Transitory tachycardia of 170 to 180 beats per minute was noted in 2 of the fetuses in this study following episodes of bradycardia and irregularity thought to be related to very strong and frequent uterine contractions. This tachycardia may be the result of lesser degrees of hypoxia which

Fig. 2, A, B, and C).  
C, Prolonged and profound bradycardia associated with a longer uterine contraction and more prolonged compression of the umbilical cord (same patient as in Fig. 8, A). In addition to the bradycardia probably due to vascular reflexes and altered fetal hemodynamics (Fig. 8, A), a hypoxic component (Fig. 8, B) is probably present.

are produced over a relatively long period of time (minutes). Similar tachycardia followed the episode of bradycardia and irregularity associated with maternal syncope (Fig. 7, A). From the records discussed here and other findings to be reported in connection with maternal oxygenation studies, fetal tachycardia of this magnitude which reaches 160 to 180 beats per minute following a hypoxic episode appears to be the earliest sign of mild fetal embarrassment. Such a conclusion appears to be supported by the work of Reynolds and Paul<sup>11</sup> who lowered the oxygen content of air given to ewes and usually noted fetal tachycardia with mild degrees of maternal anoxia.

### Summary and Conclusions

1. The fetal bradycardia patterns associated with umbilical cord compression differ from those associated with frequent and strong uterine contractions.
2. The fetal bradycardia noted in abnormal labor is probably hypoxic in origin and may be due to alterations in intervillous space blood flow.
3. Adequate intervillous space blood flow and oxygenation are probably related to a normal differential between intramyometrial and maternal blood pressure as well as sufficient relaxation between uterine contractions.
4. Severe fetal bradycardia and irregularity were noted with maternal syncope.
5. The fetal bradycardia pattern noted in a hypotensive patient with caudal anesthesia is similar to that associated with frequent and strong uterine contractions.
6. The pathologic fetal bradycardias which are not associated with poor condition of the infant at birth may be classified, clinically, as marginal bradycardias and thereby connote a warning of probable, rather than actual, fetal difficulty.
7. A U-shaped pathologic fetal bradycardia pattern which is becoming progressively longer in duration and associated with irregularity probably indicates poor fetal environment.
8. Fetal tachycardia, 170 to 180 beats per minute, may indicate slowly developing mild hypoxia.
9. The fetal bradycardias associated with frequent and strong uterine contractions and maternal hypotension are probably of more serious import than similar degrees of bradycardia noted with umbilical cord compression.

I wish to thank the research nurses, secretarial, and electronic personnel for the patient and persevering work which has made this study possible. The willing cooperation of the nursing and resident staffs of the Grace-New Haven Community Hospital is also much appreciated.

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## A METHOD OF FETAL ELECTROCARDIOGRAPHY\*†

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INTEREST in fetal electrocardiography is almost as old as the electrocardiograph itself. Not long after a practical system of recording the action potentials of the human heart was described by Einthoven,<sup>10</sup> the possibility of doing the same for the heart of the unborn fetus was investigated. Cremer,<sup>6</sup> in 1906, succeeded in recording the electrocardiogram of the fetus of a patient at term, using a string galvanometer with an abdominal and a vaginal lead. Since that time the attempts of the different workers have met with variable success.<sup>1-5, 7-9, 11-29</sup> Almost every conceivable placement of electrodes has been tried, including esophageal, vaginal, rectal, abdominal, endouterine, as well as ordinary limb leads. The increased sensitivity obtained by the introduction of the vacuum tube amplifier by Maekawa and Toyoshima<sup>18</sup> in 1930 made it possible to obtain a fetal tracing with the use of leads on the abdomen. In 1942, Ward and Kennedy<sup>28</sup> used electroencephalographic equipment to obtain tracings earlier in pregnancy. In recent years with improved equipment, fairly reliable and consistent results have been obtained, especially during the latter months of pregnancy.<sup>3, 24, 29</sup> Southern<sup>25</sup> has pointed out a possible relationship of fetal anoxia to changes in the fetal electrocardiogram. Skemp and Millen<sup>22</sup> in a recent article cite several cases where the fetal electrocardiogram was found useful, particularly when fetal death in utero had been suspected. They consider electrical evidence of fetal heart activity as the fourth positive sign of pregnancy.

The clinical potentialities of the fetal electrocardiogram were noted early in its history by various workers, including Strassman,<sup>26</sup> Dressler and Moskowitz,<sup>8</sup> Goodyer, Geiger, and Monroe,<sup>11</sup> and others. In 1938, Bell,<sup>1</sup> not very enthusiastic with his results with the equipment available at that time, still made the pertinent observation, "It can at least be said in its favor that, unlike so many biological tests for pregnancy, it would not be expected to produce any false positives." With improved equipment and better results of later series, this observation has been borne out and finds general agreement among those in this field. Not only as a test for pregnancy, but as an indication of the presence of a live fetus, it is considered most reliable in the cases where a positive result has been obtained.

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†Taken in part from a thesis submitted by Dr. Walter to the School of Medicine in partial fulfillment of the requirements for the degree of Doctor of Medicine.

This paper concerns the equipment and technique we have used, results in normal pregnancy, some specific clinical applications, and some of the factors that interfere.

### Equipment and Technique

The following is a list of the specific equipment used, with pertinent specifications and adjustments.

1. *Recording Unit.*—The recording unit of the system, a Sanborn Twin-viso Model 60-1300, is a two-channel, direct writing electrocardiograph with a third stylus that records 1 second intervals or marker pulses as needed. One channel records the voltage from abdominal leads containing the fetal impulses, while the other channel simultaneously records the maternal standard Lead I. The latter is considered desirable to facilitate the identification of the maternal complexes that appear in the tracing from the abdomen, but is not absolutely necessary. A choice of paper speeds between 0.5 and 100 mm. per second is available. A paper speed of 25 mm. per second was found generally satisfactory. The galvanometers are D'Arsonval moving coil type movement with a writing arm fastened to the coil with a hot-wire stylus at the end. The deflection sensitivity is best set at 10 mm. per millivolt. Since the magnitude of the fetal heart potentials is small, it is necessary that a preamplifier be used to amplify the abdominal lead voltage before transmission to the recorder. The over-all gain of the system is controlled by the setting of the attenuator of the electrocardiograph. The usual range of the over-all sensitivity varied from about 10 microvolts per millimeter with the attenuator set at  $\times 20$  to about 2.5 microvolts per millimeter with the attenuator set at  $\times 5$ . Power to the Sanborn is supplied by 110 volts A. C. and this unit is best separated from the preamplifier by at least several feet to reduce the pickup of A. C. interference.

2. *Preamplifier.*—The Grass Model P5, which was designed for electroencephalography, has a peak amplification of 28,000, with push-pull input. The inherent noise level is about 5 microvolts with a wide band pass, and is about 1 microvolt with a narrow band setting of the filters. The dial settings listed were found satisfactory:

Attenuator: Down two steps (-6db)  
Amplification: 28,000  
Filter: (Half-amplitude frequencies)  
Low: 7 cps      High: 100 cps

The power to the preamplifier is supplied by batteries because of their lower noise. The filaments are supplied by an Exide battery, type 3PLX-13, which is a low specific gravity type 6 volt storage battery. Its low noise characteristics are superior in this type application. Leads were soldered directly to the terminals to eliminate a possible source of noise. The higher voltage B supply consisted of two Burgess No. 5308 low noise 45 volt batteries. A battery charger was used for the storage battery. The leads from the abdominal electrodes to the preamplifier were shielded and were shorter than the maximum allowable 4 feet.

3. *Ohmmeter.*—A Simpson Model 260 was used to measure the electrode to skin resistance.

4. *Screen Wire Cage.*—This was found useful in reducing interference from a nearby television station, and other extraneous electrical noises, but in electrically quiet locations it is not necessary. The cage measured 6 by 6 by 8

feet, and contained the patient on a roller, and a steel table with the preamplifier and its power supply. The Sanborn Electrocardiograph Recorder was left outside.

5. *Electrodes.*—The four electrodes are of usual electrocardiograph design. They are slightly curved, measuring 3 by 5 cm., with a binding post and a lug for the rubber straps which hold them in place. They are supplied with the Sanborn. Also supplied are the rubber straps, two measuring 45 cm. for the arm electrodes and two 150 cm. long to hold the abdominal leads in place.

6. *Electrode Paste.*—Sanborn Redux was used.

7. *Recording Paper.*—Sanborn two-channel paper was used.

8. *Miscellaneous.*—This includes a hospital roller for the patient, a steel table for the preamplifier and its power supply, shielded cables, and a careful system of ground wires to connect together the chassis of each of the units and the steel table to ground, without loop circuits. The total cost of the entire installation was under \$2,000.00.

The technique employed in taking the fetal electrocardiogram was kept as simple as possible. Electrodes were placed directly upon the abdomen with no attempt made to place them in any of the body orifices. No sedation or other medication was used. In this way the procedure could easily be done by a technician and the patient could be sent home directly upon completion of the test.

After the patient emptied her bladder, she was placed on the roller in the supine position. Electrode paste was applied to her wrists and the arm electrodes placed in position. These were then connected directly into one channel of the Sanborn to record the maternal Lead I. The lower abdomen was then exposed and examined to determine the best position for the abdominal electrodes. The particular placement of electrodes varied somewhat. In early pregnancy when the uterus is low in the pelvis, best results were obtained with both the electrodes in the midline. The lower was placed near the pubic symphysis and the upper was placed directly superior to it, approximately over the fundus. In later months the superior electrode was moved higher and placed over the most prominent part of the fetus. On occasion it was found helpful to place the electrodes in an oblique or transverse position. Vaginal emplacement of one electrode has not been satisfactory in our experience.

The Redux electrode paste was applied to the selected areas of the skin of the abdomen and massaged with a tongue depressor. The electrodes were emplaced and the direct current resistance between electrodes measured with the ohmmeter. The quality of the skin to the electrode contact varies inversely with the resistance and if it was found high (over 1,500 ohms) alcohol or ether was used to prepare the skin before the electrode paste was again applied. Considerable effort was expended to keep resistance at a minimum. The electrodes were then connected to the shielded wires leading to the preamplifier. We have not found it necessary to ground the patient.

With everything ready, the operator left the shielded cage and went to the recorder, which is kept outside to reduce noise. A calibration of the standard 1.0 millivolt signal is placed on the tracing. The tracing is then made and the sensitivity is increased by varying the attenuator on the Sanborn, until the fetal complex appears or the tracing is obviously negative. If the skin resistance previously measured was satisfactory, another position of electrode placement may be tried before a negative result is concluded. The time taken for the entire procedure was from 15 to 45 minutes.



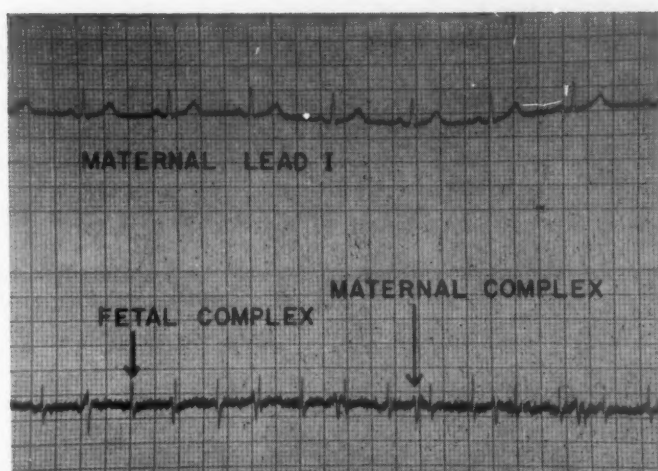


Fig. 1.

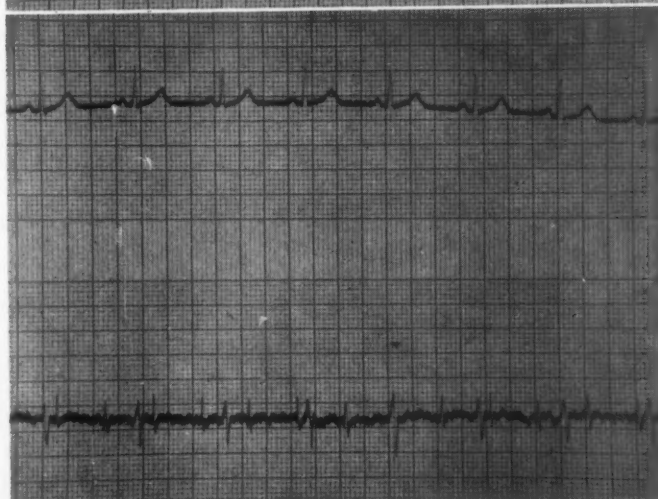


Fig. 2.

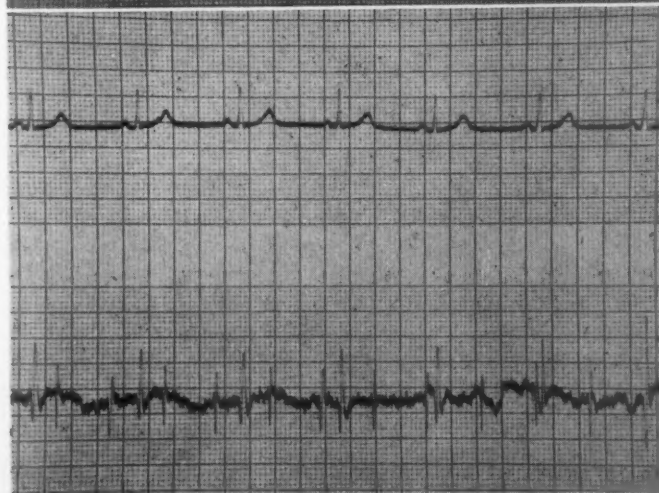


Fig. 3.

Fig. 1.—Patient C. P. at 22 weeks' gestation.  
Fig. 2.—Patient C. P. at 28 weeks' gestation.  
Fig. 3.—Patient C. P. at 33 weeks' gestation.

Examples of good quality positive tracings are illustrated in the photographic reproductions labeled Figs. 1, 2, and 3. The upper channel is the maternal Lead I. The lower is from the abdominal leads and contains both the maternal and the fetal complexes. These tracings are from the same patient and represent 22, 28, and 33 weeks' gestational age, respectively. Fig. 4 illustrates interference from a television station, and Fig. 5 shows the interference from an anxious patient.

#### A Survey of 95 Cases of Normal Pregnancy

This part of the study was made to determine the percentage of positive electrocardiograms that can be obtained at various times during the normal

Fig. 4.

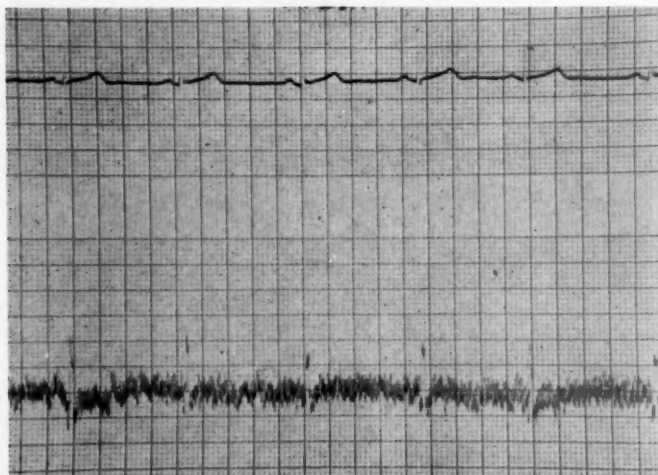


Fig. 5.

Fig. 4.—Interference caused by nearby television transmitter.

Fig. 5.—Interference seen with an anxious patient.

pregnancy. The criteria of a positive tracing have already been discussed in the literature.<sup>3, 8</sup> In this survey a positive fetal electrocardiogram is one in which at least the R wave of the QRS complex is easily recognizable, with a rate, regularity, persistence, and magnitude such that there is little question of its confusion with artifacts. The patients were chosen to represent a random sample of normal pregnancies from the Obstetric Clinic and Charity

Hospital, New Orleans, with the only qualification that they have an apparently normal pregnancy. Cases were chosen from as early as 7 weeks' up to 37 weeks' gestational age.

The results are shown in Fig. 6. The first attempt only is tabulated. Repeating the procedure at another time increases the number of positive results, probably because the patient is less apprehensive. Thus, we feel that these figures represent minimal accuracy with this technique. The earliest positive tracing was obtained in a fetus with a gestational age of 12 weeks. One hundred per cent positive tracings were obtained over 34 weeks. Since all 94 patients were later proved to have live babies, the negatives are false negatives. No false positives were obtained in this survey, or at any other time.

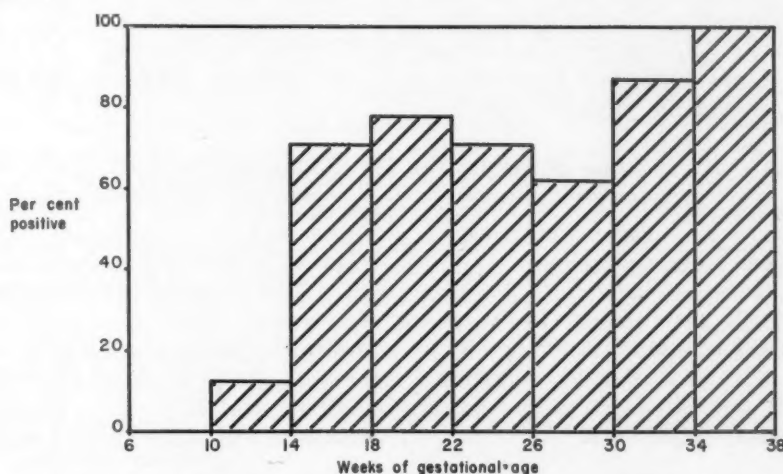


Fig. 6.—Results of the first attempt to obtain a fetal electrocardiogram in 94 normal cases.

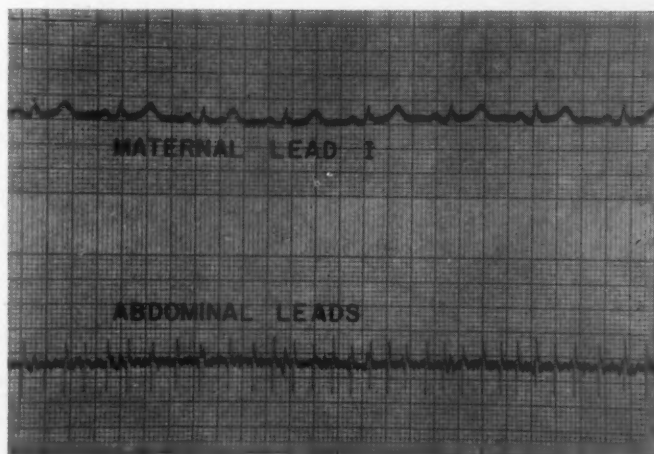


Fig. 7.—Unidentified rapid impulses.

It was noted several times in very early pregnancy (about 9 to 14 weeks) that a very fast, regular series of impulses appeared on the tracing. These were in the order of 250 to 500 impulses per minute. Were it not for the very fast rate involved, these might be confused with the usual fetal R wave. They have been observed simultaneously with the fetal QRS. Whether these impulses represent muscle activity or have some other significance is not clear at this time. An example is shown in Fig. 7.

### Clinical Applications

The most important clinical use of the fetal electrocardiograph at this time is in proving the presence of a live fetus where this might be doubted on clinical evidence and a diagnosis is important at the time, for example, when there is doubt about the diagnosis of pregnancy and the biological tests are positive. Such a situation could be due to a hydatidiform mole or a dead fetus, and a fetal electrocardiogram would be helpful in establishing the correct diagnosis and would influence the management of the case, particularly if it is positive. A fetal electrocardiogram can give a positive result before the fetal skeleton is visible on x-ray, and since its use is without the hazards of radiation, it may be done whenever and as often as is desired. A diagnosis is useful in cases of suspected fetal death in utero. A positive fetal electrocardiogram is excellent proof of the presence of a live fetus at any time, even in the absence of fetal heart tones or detectable fetal movements.

In Table I are recorded 10 clinical cases in which a fetal electrocardiogram was requested by the clinician.

TABLE I. TEN CLINICAL CASES IN WHICH THE FETAL ELECTROCARDIOGRAM WAS USED

CASE NO.	GESTATIONAL AGE	CLINICAL DIAGNOSIS	RESULT OF FETAL ECG	OUTCOME
1	26 weeks	Fetal death	Negative	Aborted 3 pound, 4 ounce macerated fetus 4 weeks later
2	20 weeks	Fetal death	Positive	Delivered 8 pound, 2 ounce viable infant 18 weeks later
3	15 weeks	Fetal death	Negative	Leiomyoma found on exploratory operation
4	29 weeks	Fetal death	Negative	Delivered 5 pound, 5 ounce viable infant 6 weeks later
5	30 weeks	Fetal death	Negative	Delivered a macerated fetus 3 weeks later
6	14 weeks	Tubal ectycesis removed at 6 weeks, possible intra-uterine pregnancy	Positive	Delivered viable infant 18 weeks later
7	29 weeks	Rh incompatibility, fetal death, pre-eclampsia	Positive	Living infant delivered by cesarean section 2 weeks later, died 2 hours after delivery
8	15 weeks	Hypertension, possible hydatidiform mole	Positive	Delivered 6 pound, 9 ounce viable infant 18 weeks later
9	18 weeks	Hydatidiform mole	Negative	Pitocin induced delivery of mole 1 week later
10	34 weeks	Possible twins	Twins	Viable twins delivered 3 weeks later

### Comment

Although a positive tracing is quite reliable, the significance of a negative result is more equivocal. Various factors tend to cause a false negative result. Most of these have been previously noted.<sup>4, 11</sup> The following is a list of those found important in this investigation:



*Time of Pregnancy.*—See Fig. 5. In early pregnancy and again at about 28 weeks false negatives are more common.

*High Skin Resistance.*—The resistance between electrodes and skin as measured by the ohmmeter was found quite important. The upper limit of resistance compatible with a positive result was variable, but in general a resistance over 1,500 ohms gave poor results. Typical values on positive tracings were between 500 and 1,000 ohms. Occasionally it was as low as 200 ohms, and sometimes a figure as high as 3,000 ohms gave a positive result.

*Electrical Interference.*—This may arise from other electrical equipment in the vicinity, or may be caused by local broadcasting stations. The shielded cage previously described was very helpful in eliminating outside interference.

*Other Factors.*—Other factors that decrease the likelihood of a positive tracing are a full bladder, obesity, position of the placenta, polyhydramnios, multiple pregnancy, apprehension, and the fetal position.

If none of these more obvious interfering factors is present, then a negative result during the last trimester would be fairly strong evidence against the presence of a live fetus, but would not be conclusive. Referring again to Fig. 5, it is apparent that a negative result has much less significance earlier and little, if any, meaning before 12 weeks. Of course, a positive tracing is quite conclusive at any time.

The clinical value of fetal electrocardiography today lies in its ability to establish the presence of a live fetus. If the percentage of positive tracings obtainable in early pregnancy could be increased, then its usefulness would be greatly extended. As better electronic equipment becomes available and the technique of fetal electrocardiography improves, it may become possible consistently to obtain positive tracings at a much earlier time than is possible today, with fewer false negatives.

### Summary

The equipment and a technique for fetal electrocardiography are described in some detail. A survey of the results in normal pregnancy is reported. Clinical applications are discussed, and 10 cases are reported.

### Conclusions

1. The fetal electrocardiograph is a practical device that is particularly useful in establishing the presence of fetal life when it is important to make this diagnosis and other means cannot be used.

2. A positive result is acceptable proof that a live fetus is present. The evaluation of a negative result is more difficult because of the occurrence of false negatives. A negative result is more significant during the last weeks of pregnancy.

3. Technique is most important in fetal electrocardiography. The particular technique described in this paper seems best in our hands for this equipment.

4. Improvements in amplifying and recording systems will remove many of the present difficulties; nevertheless, fetal electrocardiography is useful now.

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## THE FETAL ELECTROCARDIOGRAM IN MULTIPLE PREGNANCY\*

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**A** MOST useful aspect of fetal electrocardiographic technique, as it is now emerging, is the information provided in instances of multiple pregnancy. The few reports in the literature<sup>1, 2</sup> of twin pregnancies as demonstrated by the fetal electrocardiogram showed technical improvement over Cremer's<sup>3</sup> first demonstration (Fig. 1) of a fetal electrocardiogram. In this paper it will be shown that twin and other multiple pregnancies can be demonstrated clearly by the fetal electrocardiogram, that early diagnosis is possible, and that useful allied studies can be made.

### Materials and Methods

In this study, 11 multiple pregnancies including 9 twin pregnancies, one triple, and one quadruple pregnancy have been studied. Since the technique of recording the fetal electrocardiogram has been reported,<sup>4</sup> it will be summarized, only, at this point. The equipment used has been one of more channels of an Offner multichannel high sensitivity, direct writing oscillograph. A type 9406 preamplifier is used to bring the sensitivity into the microvolt range, as is necessary for this work. German silver or nickel electrodes are used and skin preparation is similar to that with standard electrocardiographic techniques. Electrode positions are important. A standard midline pair is used routinely with one electrode placed just above the umbilicus, and the other just above the symphysis. Horizontal pairs are sometimes used, as when a transverse lie is suspected. A second useful lead is an anterior-posterior pair; in this instance, the anterior lead is placed just above the umbilicus, and the second electrode is placed in the midline of the lumbar region, approximately 10 cm. above the coccyx. Occasionally it is desirable to shift this electrode a few centimeters laterally to minimize background noise. In another important variant of this pair the anterior electrode is placed on the fundus of the uterus. A unipolar pair is often used with the exploring electrode on the uterine fundus and the lower electrode on the thigh.

It has been found that the position of the patient is of importance. For this reason the recording is done in dorsal, lateral, and ventral positions. It has been found that some of the most successful recordings have been obtained with the patient in the ventral, face-down position.

For the purpose of standardization, electrode polarities have been so chosen that the f-QRS is upright when the fetus is presenting by the vertex. With this convention, the maternal QRS is directed downward (Fig. 2).

\*This research was supported by a grant-in-aid from the United States Public Health Service, RG-4462.

## Results

*Definitions.*—

1. f-ecg: The fetal electrocardiogram in utero.
2. f-QRS: The fetal QRS complex as observed with short time constants as in this investigation, hence a somewhat more specific nomenclature.
3. Electrical axis of the heart: Vector visualizing the resultant of all the differences of potential within the heart at the moment of the greatest deflection of the QRS complex.

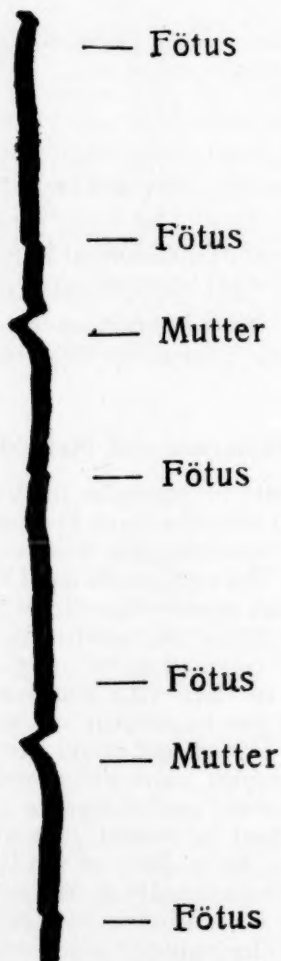


Fig. 1.—Cremer's demonstration of the fetal electrocardiogram in 1906. The fetal complexes can be located by the break in the baseline at the indicated points.

In order to lay the basis for understanding, typical fetal electrocardiograms recorded for single vertex and breech presentations are shown in Figs. 2 and 3. Fig. 2 shows that the f-QRS in vertex presentations is upright, clearly seen, and oppositely directed to the maternal complex. Fig. 3 shows that the f-QRS in breech presentations is equally clear, but is directed downward, i.e., in phase with the maternal complex, since the electrical axes of the fetal and the maternal heart are more or less in the same direction under such conditions.





Fig. 2.—Three examples of the fetal electrocardiogram with the fetus in vertex presentation. The large maternal complexes are directed downward and the fetal complexes occur at a faster rate and are directed upward.

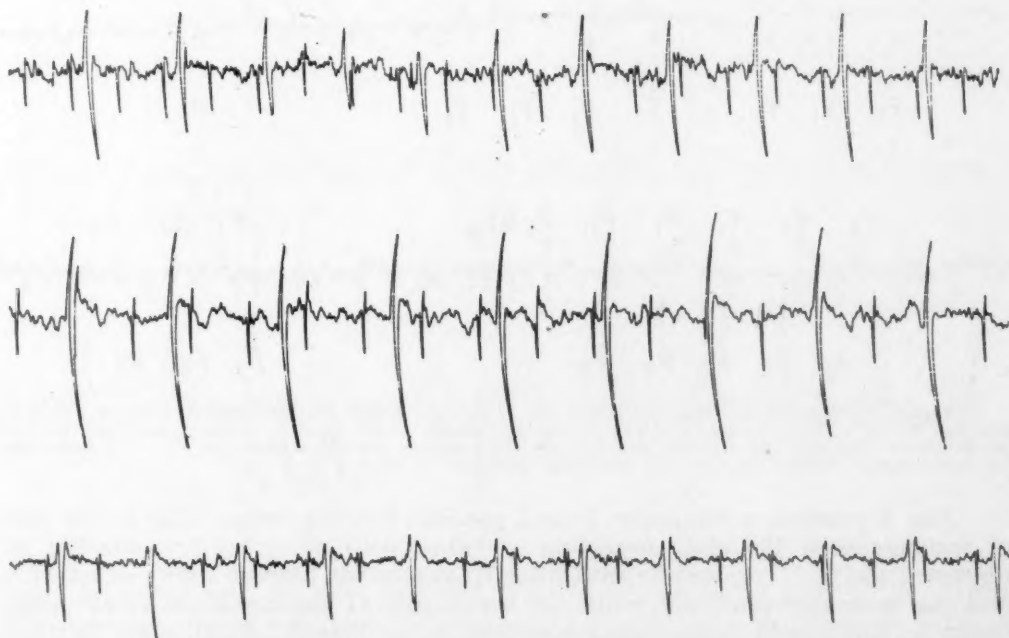


Fig. 3.—Three examples of the fetal electrocardiogram with the fetus in breech presentation. Since the electrical axes of the maternal and fetal hearts are essentially in the same direction, both the maternal and fetal complexes are directed downward.

With these recordings as a basis, Fig. 4 shows a typical example of the fetal electrocardiogram in a twin pregnancy. A regular succession of fetal complexes  $F_1$  can be followed through the tracing, as can an independent set of fetal complexes  $F_2$ . The primary direction of the fetal complexes is upward, indicating that both fetuses are presenting by the vertex. At delivery, 2 viable infants were born by vertex presentation. Fig. 5 shows a diagnosis of twin pregnancy made from a tracing obtained at the sixteenth week of pregnancy. Even at this early stage of gestation pairs of fetal complexes can be followed through the tracing. The diagnosis of twins was confirmed by the fetal electrocardiogram at 21 weeks (Fig. 5, lower tracing), by radiological means shortly thereafter, and by the eventual delivery of twins.

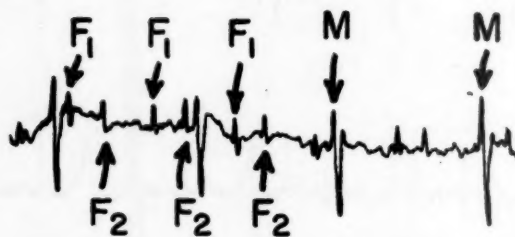


Fig. 4.—Twin pregnancy as demonstrated by the fetal electrocardiogram. Both fetuses are presenting by the vertex, hence the fetal complexes are directed upward. Twins were born, both presenting by the vertex at delivery.

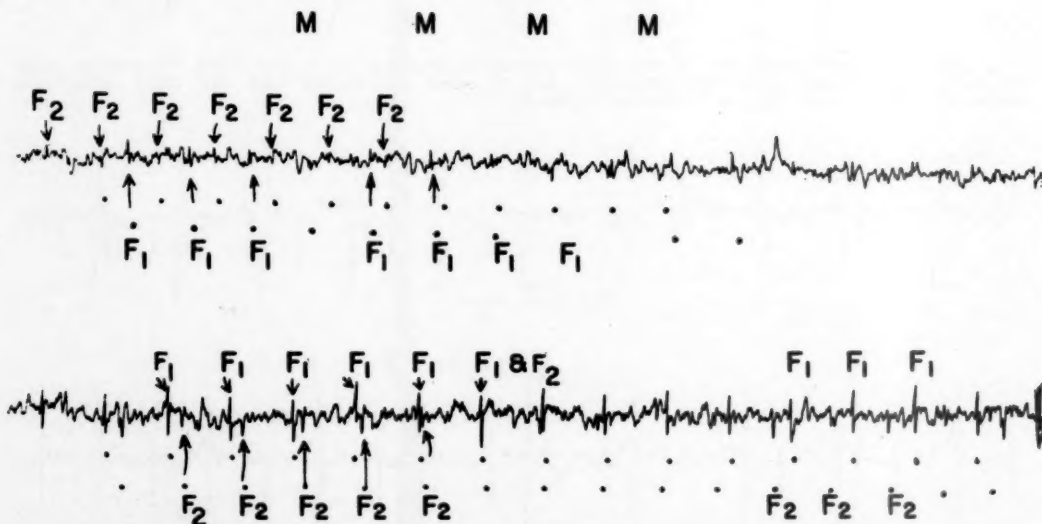


Fig. 5.—Diagnosis of twin pregnancy at 16 weeks by the fetal electrocardiogram. Upper tracing, at 16 weeks. Lower tracing, the same patient at 21 weeks. Fetal complexes  $F_1$  can be followed through the tracing as can an independent set of complexes  $F_2$ . Confirmation by radiological means and by the eventual delivery of twins.

Fig. 6 presents a composite from 3 patients bearing twins. The upper pair of tracings show the clear recording of twins, both in vertex presentation, as discussed above. The middle recording from another patient shows one vertex and one breech presentation, while the lowest pair of tracings show a twin pregnancy in which both fetuses are presenting by the breech. In all cases delivery of 2 infants took place.

Fig. 7 shows recordings from a triple and from a quadruple pregnancy. These tracings, while not as clear technically (recording was not under optimal conditions) because of patient discomfort and other reasons, nevertheless show the presence of three and four fetal complexes.

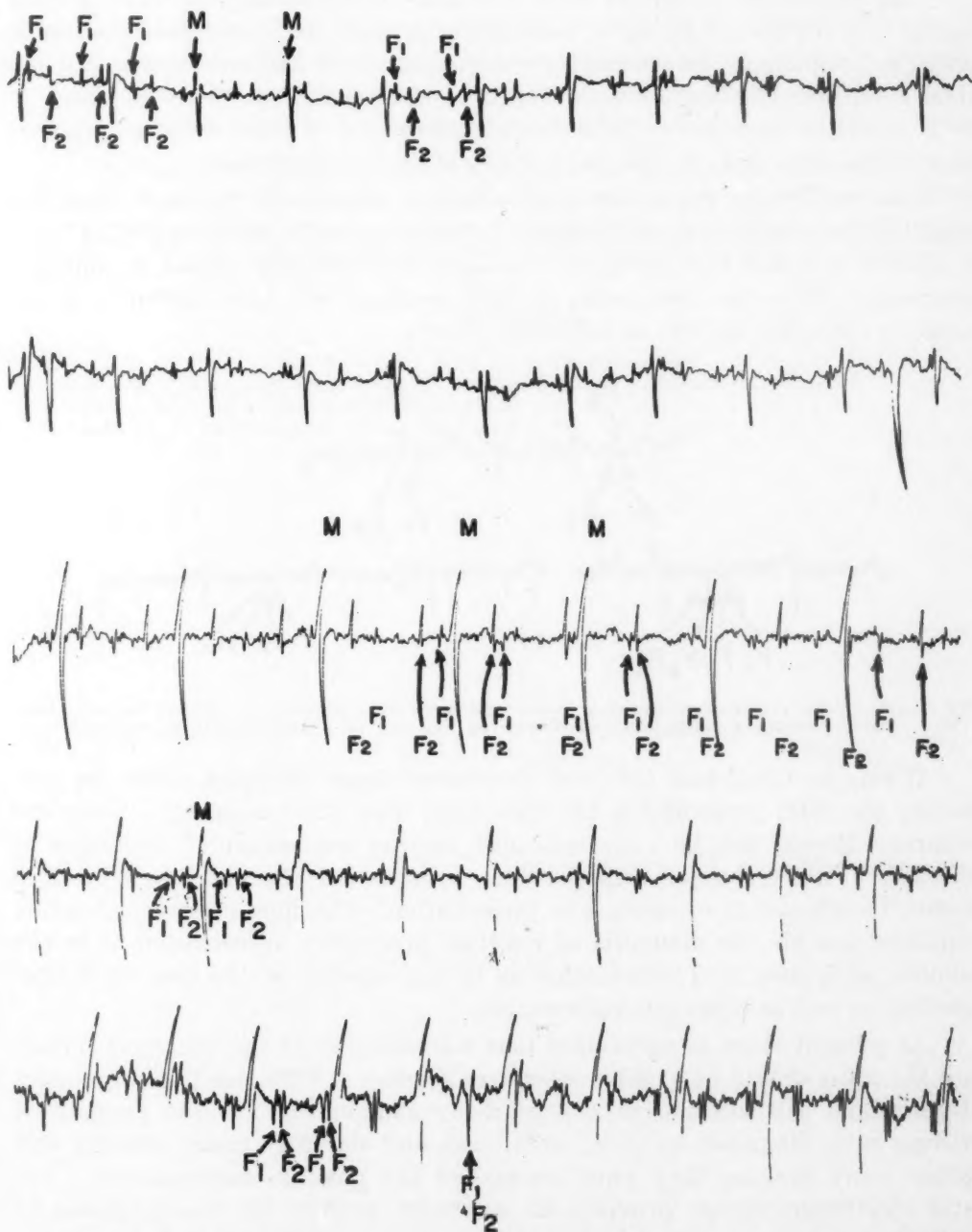


Fig. 6.—Effect of fetal position on the fetal electrocardiogram in twin pregnancies. Upper 2 tracings show the clear recording of twins, both in vertex presentation. Middle tracing shows one vertex and one breech presentation. Lower 2 tracings show the fetal electrocardiogram when both fetuses present by the breech. Note the diagnostic value of superposition when a double spike is obtained if both fetuses present in the same way (point marked F<sub>1</sub> and F<sub>2</sub>).

### Comment

The recordings presented show the fetal electrocardiogram to be a most useful tool for the diagnosis of multiple pregnancy and fetal presentation in multiple pregnancy. In previously reported work,<sup>4</sup> it has been shown that the fetal electrocardiogram becomes large and clear rather suddenly at about 19 to 21 weeks of pregnancy. It is possible, therefore, to make definite diagnoses of multiple pregnancy at this stage of gestation, or even earlier.

The fetal heart rates can be determined accurately, for each fetus, by counting the number of fetal complexes per 10 seconds and multiplying by 6. It should be noted that integrator methods are probably useless in multiple pregnancy, since the instrument in such methods will have difficulty in accurately following the two or more fetal hearts.

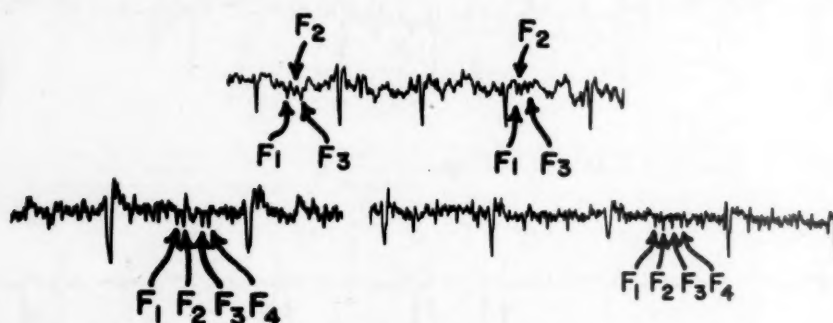


Fig. 7.—The fetal electrocardiogram in triple and quadruple pregnancy. Upper tracing, triplets. Lower tracing, quadruplets. Confirmed by delivery of 3 and 4 infants, respectively.

It may be noted that the fetal electrocardiogram provides means for estimating the fetal presentation for each fetus with great accuracy. Complete accuracy should not be expected until further perfection of technique is effected. This technique also provides a means of studying, by objective means, the frequency of changes in presentation. The fetal electrocardiogram can thus provide the diagnosis of multiple pregnancy, information as to the number of fetuses, and information as to presentation at the time of the recording, as well as heart rate information.

At present there is agreement that x-irradiation of the pregnant female and the fetus should be avoided whenever possible. With this thinking, many obstetricians will hesitate to request x-ray examination for the purpose of making such diagnoses as those mentioned, and similarly many patients will refuse x-ray because they have learned of the possible consequences. The fetal electrocardiogram provides an alternate method for the diagnosis of multiple pregnancy, a method which is completely safe and free from criticism, a method which can be repeated as often as necessary without contraindication.

### Summary

1. The fetal electrocardiogram is shown to be a useful tool in the study of multiple pregnancy.



2. Recordings from 9 sets of twins, one set of triplets, and one set of quadruplets are presented.

3. Diagnosis of a twin pregnancy at 16 weeks is demonstrated.

4. The possibility of studying the presentation of the fetuses is discussed.

5. The fetal electrocardiogram is suggested as an alternate method of diagnosis when x-ray technique may not be desired.

The help extended to this research, through the provision of material, by Drs. W. Dignam, W. Hindle, J. Moore, D. G. Morton, W. Newswanger, W. A. Selle, and J. Voskian, is gratefully acknowledged. Appreciation is expressed for the provision of facilities by the obstetric staffs of Harbor General Hospital and the Teaching Hospital, the Medical Center, U.C.L.A.

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## PRENATAL FETAL ELECTROENCEPHALOGRAPHY

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**T**HE DIAGNOSIS and treatment of human illness concern all physicians. In addition, the obstetrician and, to a limited extent, the pediatrician, are involved in the prophylaxis and active therapy of derangements of normal functions of the unborn child from the time of conception to those moments when adjustment to extrauterine life is completed. The complex development from the stage of the fertilized ovum to the full-term fetus and finally the newborn infant proceeds in an orderly and undisturbed manner in many instances. In these cases, the care of the intrauterine fetus does not present problems which cannot be solved satisfactorily without additional aids. The other group of pregnancies are of a complicated nature and the physician caring for the mother and her unborn child may need all the facilities which modern medicine can provide. These techniques include both those which are applicable in studying the fetus while it remains in the uterus and those which are limited to the evaluation of the newborn infant. Among the tests which are of value in studying the fetus in utero are roentgen studies, fetal electrocardiography, and fetal electroencephalography. Roentgen studies give only indirect evidence of fetal difficulties. Fetal electrocardiography is noteworthy for investigation of changes in the rate and rhythm of the fetal heart. Fetal electroencephalography is a sensitive test which may yield information characteristic of anoxic states in the fetus; subtle changes will be evident in the electrical activity of the brain.

### Historical Background

Approximately 18 years ago, Lindsley<sup>3</sup> studied the electric potentials obtained from the abdomen of a pregnant woman at term. He found that by placing the electrodes close to each other, he was able either to completely screen out maternal electrical activity or greatly to reduce its amplitude. By this method he discovered and first recorded electrical activity from the brain of the fetus not yet removed from the uterus. This discovery remained in obscurity until Bernstine, Borkowski, and Price<sup>1</sup> performed the same procedure in a larger series of cases. In addition, they improvised several vaginal electrodes for the purpose of obtaining intrauterine fetal electroencephalograms.

The study of the fetus once removed from its maternal environment is closely allied with the above work. Whether the fetus has been situated in the

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uterus or in such extrauterine sites as the tubes or ovaries does not influence the electrical activity of the brain, provided the maternal-fetal blood circulation is competent. These detailed studies are necessary to establish the concept of early development of the electrical activity of the human fetal brain.

Okomoto and Kirikae<sup>4, 5</sup> have demonstrated the electrical activity of the brain in human fetuses (3 to 7 months) and in 2 prematurely born infants (8 and 9 months). Borkowski and Bernstine<sup>2</sup> have shown the electroencephalographic tracings in human fetuses of 43 to 116 days of gestation.

### Procedure

Various technical adjustments have been made since the initial studies almost 5 years ago. Since the preliminary tests, refinements have been made in technique and in the electrodes used. In the description to follow, the regimen currently in use will be described.

Bimanual examination and catheterization of the bladder were done on all patients. The vaginal speculum electrode was inserted into the vagina. Visualization of the cervix was performed. The patient was placed in a comfortable semireclining position and standard electroencephalograph electrodes were placed on the abdomen. All electrodes were connected to a Grass eight-lead electroencephalograph machine (Model III series). Readings were chiefly bipolar. All patients were instructed to breathe deeply for 3 minutes at the conclusion of the recording.

### The Study Group

The present report covers studies carried out in 75 pregnant women. Fifty-three of these were Negro patients and 22 white. Eighteen were gravida i, 12 gravida ii, and 11 each gravida iii and iv. Seven were gravida v and 16 of the group were gravida vi or more at the time the study was carried out. The age distribution was not unlike that in the general obstetric population in this hospital. Fourteen were 20 years old or younger and the majority (41 of the 75) were between 21 and 30 years of age. Eighteen were 31 to 40 years old and 2 were over 41 years of age.

TABLE I. COMPLICATIONS OF PREGNANCY

Pre-eclampsia	
Mild	8
Severe	2
Essential hypertension	8
Epilepsy	4
Sickle cell anemia	3
Changes in fetal heart tones	
Absent	4
Increased	1
Healed pulmonary tuberculosis	1
Pyelitis	1
Previous external cephalic version	2
Inactive rheumatic heart disease	1
Intra-atrial septal defect	1
Treated congenital syphilis	1
Multiple pregnancies	2
Twins	1
Triplets	1

Most of the studies were carried out at or near term, 36 of the 75 determinations between 37 weeks and term. Eighteen of the studies were carried

out between 33 and 36 weeks and 9 were carried out at 32 weeks or earlier. Six determinations were made post term and 6 while the patient was in active labor. The coincidental complications of pregnancy are indicated in Table I. With the exception of the changes in fetal heart tone none of these complications had a direct bearing on the findings in electroencephalography.

### Results

In the 75 cases studied, 95 varieties of frequencies were encountered in the electroencephalogram pattern. Fifteen of these were superimposed on slower frequencies and 20 cases had frequencies in two groups. However, no group had frequencies in more than two groups. Table II indicates the distribution of frequencies as well as the distribution in voltages encountered and Table III indicates the response in the fetal electroencephalogram to maternal hyperventilation.

TABLE II. DISTRIBUTIONS OF FREQUENCY AND VOLTAGE

<i>Frequency</i> *†.—	
Waves per minute:	
$\frac{1}{2}$ -4	52%
4-8 $\frac{1}{2}$	32%
8 $\frac{1}{2}$ -12	14%
Greater than 12	17%
<i>Voltage</i> †.—	
High	0%
Moderate	21%
Low	68%

\*Percentage includes 20 cases with frequencies in two groups.

†Percentage does not include those cases in which no fetal electroencephalogram was recorded.

TABLE III. RESPONSE OF FETAL ELECTROENCEPHALOGRAPH TO MATERNAL HYPERVENTILATION

No change	73%
Change in voltage	19%
Increase	19%
Decrease	0%
Change in frequency	8%
Increase	4%
Decrease	4%

There were no untoward effects from this procedure. Premature labor was not induced; no local trauma to vagina, cervix, fetus, or placenta was observed. No known cases of low-lying placenta were studied. Intrauterine infection was found post partum in only one case and that was attributable to prolonged rupture of the membranes. In this case, a low-grade fever was present prior to performance of the fetal electroencephalogram. All patients studied were in the hospital for 4 to 5 days following the delivery.

The fetal electroencephalogram in approximately 85 per cent of the instances consisted of waves of low to moderate voltage at  $\frac{1}{2}$  to 12 per second. In the remaining 15 per cent the waves were small and of a fast frequency (15 to 30 waves per second). In several instances the fast rhythms were observed in infants of epileptic mothers. These observations were made while the fetus was in utero and then immediately after birth. A long-range follow-up study will indicate the prognostic significance of this aspect of the fetal electroencephalogram.

Usually there was no change evident in the fetal electroencephalogram. In 27 per cent of the cases changes were observed; 19 per cent were changes in



voltage and in 8 per cent changes in frequency. Whenever changes in voltage occurred, it was increased; the changes in frequency were equally divided into increases and diminutions. Following the cessation of hyperventilation, the return to previous activity was rapid. In 3 cases there was no immediate return and in one case a slow return after the appearance of abnormal activity. The latter case follows:

CASE 1.—F. D., a 34-year-old Negro woman, gravida vi, para iii, was 4 weeks past the expected date of delivery.

At the time of the first test no fetal heart sounds were heard. The vaginal electrodes were applied under direct vision upon the head of the fetus. Fetal electrocardiogram was absent. Fetal electroencephalogram revealed small waves at 6 per second from both vaginal and abdominal leads. Hyperventilation of the mother for 3 minutes produced a pronounced build-up in voltage (60 microvolts).

Two and one-half days later, the test was repeated. At this time vaginal examination revealed a presenting head which was soft and flabby. Spalding's sign was positive. No fetal electrocardiogram or electroencephalogram was observed. The next day a macerated stillborn fetus was delivered spontaneously.

This activity has been observed in young fetuses and in anencephalic monsters who were in the "process of dying." These waves appear rather early in the anoxic state and do not disappear until late, although their appearance is less frequent and their voltage not as great when the anoxia is pronounced and of long standing.

In 2 of the 3 instances where cessation of hyperventilation failed to produce a return to previous frequency, the change was subtle and associated with fast activity. One of these mothers was epileptic. Both infants were healthy at birth. We feel that follow-up study is necessary prior to any decision as to the significance of these changes.

CASE 2.—C. O., a 21-year-old Negro woman, gravida iii, para ii, whose last 2 pregnancies and the interval between them had been complicated by hypertension. Her first pregnancy was terminated by cesarean section for disproportion. The second pregnancy resulted in intrauterine fetal death prior to labor. In the present pregnancy, the blood pressure varied from 140/100 to 210/140. The various systemic evidences of prolonged hypertension were present. Fetal electrocardiogram was present. Delivery by cesarean section produced a living mature male infant in no acute distress.

The fetal electroencephalogram during hyperventilation of the mother showed slowing of the dominant rhythm and the appearance of superimposed small waves at 8 per second, the voltage increased moderately. Following the discontinuation of hyperventilation, these changes persisted and further slowing of rhythm occurred. These changes are interpreted as indicative of deranged fetal cerebral metabolism.

### Summary

1. A report of approximately 5 years' experience with the study of fetal brain action potentials has been made.
2. Attention is drawn to the results which indicate the value of this procedure in assessing the condition of the fetus in utero.

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## THE MEASUREMENT OF FETAL OXYGEN\*

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THE investigative interests of a medical discipline are ordinarily determined by the problems currently unsolved in clinical practice. Thus, as 50 years of prenatal care and the application in obstetrics of therapeutic advances common to all branches of medicine have reduced maternal hazard to the negligible, at least in the Western World, emphasis in obstetrics has shifted to the fetus and newborn. Further, the concomitant reduction in mortality among term infants has resulted in increased concern over the lesser degrees of damage such as developmental abnormalities and prematurity. Specifically, this has turned attention to the availability of oxygen to the growing fetus.

Clinical and investigative thought on this subject, as is often the case when data are few, has in part been dominated by an ingenious analogy drawn 25 years ago by Sir Joseph Barcroft<sup>1</sup> between the fetus and the adult at high altitudes in regard to conditions of oxygenation. Despite the limitations of the analogy,<sup>2</sup> it has pointed to a fruitful area of speculation and investigation. Geoffrey Dawes,<sup>3</sup> a distinguished fetal physiologist, points out that "it has become fashionable to talk about anoxia or hypoxia of the fetus and newborn." One detects a note of complaint which is likely to be based on the fact that there is not at this moment a satisfactory definition of these terms. Anoxia, implying as it does the absence of oxygen, or at least its absence in excess of what may be expected from the simple diffusion of the gas through tissues, is not experienced by the fetus except upon total cessation of placental exchange or the death of the mother. Anoxia is, therefore, not a very useful term physiologically. Hypoxia, which inherently implies consideration of the *degree* of oxygen lack, is a vastly preferable term but not without its difficulties. Despite Barcroft's analogy, it makes no more sense to describe the normal fetus as hypoxic than it does to refer to an infant as hypotensive because its blood pressure is lower than that of an adult. The accurate use of words like hypoxia requires a knowledge of the range of normal values in quantitative terms. Certainly, the observations of Westin<sup>4</sup> on the early human fetus seen in the hysteroscope do not support the assumption that the fetus is hypoxic, but these are not quantitative studies.

Fortunately, largely as a result of the efforts of the respiratory physiologists, we are approaching a quantitative estimation of hypoxia. As Kety<sup>5</sup>

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pointed out in opening a recent symposium on the subject, "The maintenance of an optimal oxygen tension about each cell is one of the cardinal functions of the circulatory and respiratory systems of higher animals." The crucial words are "optimal oxygen tension about each cell." Our attention is directed to the cell rather than the inspired air, or pulmonary vein blood, or the heart rate, all of which are indeed parameters but not the crucial variable. Further, we are reminded to consider oxygen tension since, so far as is presently known, there are no special pumps or valves for oxygen, and the gas moves from air to blood and from blood to tissues in strict accordance with the physical laws of partial pressure. It is, therefore, the pressure gradient of oxygen with which we are concerned. Finally, it is clear that the optimal value must be known before a term like hypoxia can be meaningfully used. Aerobic metabolic processes proceed undiminished over a wide range of oxygen pressures.<sup>6</sup> The optimal value lies somewhere within it and may spread over a considerable range of oxygen tensions.

To put the estimation of tissue oxygen tension in more precise terms, the Krogh-Erlang equation, which is admittedly only an approximation, has proved most useful.<sup>5</sup> This may be stated as:

$$p_x = p_o - \frac{m}{d} \left( \frac{R^2}{2} \ln \frac{x}{r} - \frac{x^2 - r^2}{4} \right)$$

where:  $p_x$  = the oxygen pressure at a point in a tissue  
 $p_o$  = the oxygen pressure in blood at the beginning of the capillary bed  
 $m$  = rate of oxygen consumption  
 $d$  = diffusion coefficient of oxygen in the tissue  
 $x$  = distance from a point to the nearest capillary  
 $2R$  = intercapillary distance  
 $r$  = radius of the capillary

As Fig. 1 illustrates, the value  $p_x$  is most sensitive to changes in the intercapillary distance, since the law of inverse squares applies to movement by diffusion. It is also linearly responsive to changes of  $pO_2$  in the blood arriving in the tissue and to changes in the rate of oxygen consumption.

What information do we have at present with which to evaluate  $p_x$  for the fetus? As will be discussed further below, there are some data on  $p_o$ . Sjöstedt and Rooth<sup>7</sup> have experimented with 15 per cent oxygen atmospheres for the newborn infant and have found that they are at least tolerated. In regard to the rate of oxygen consumption, the studies of Cross and associates<sup>8</sup> have indicated, at least for the newborn infant, that as oxygen supply decreases, oxygen consumption decreases. However, Hill,<sup>9</sup> in Cross's laboratory, has now shown that this is a function of ambient temperature; if the ambient temperature is maintained near body temperature, oxygen consumption is unchanged despite decreases in oxygen supply. A constant environmental temperature may be assumed to exist in the uterus.

A most serious limitation in the application of the Krogh-Erlang equation is a lack of information about the capillary bed of the fetus. The great variability of the capillary bed and the technical problems of studying it in vivo have limited the study of even the adult structures. The studies of Räihä<sup>10</sup> on a limited number of fetal capillary networks, using dead material, suggest that the intercapillary distance in the fetus is much greater than in the adult. If this is so, the  $p_x$  for the fetus is likely to be well below the present estimates of 35 mm. Hg for adult tissues.

Let us turn our attention to what is known about the oxygen supply of the fetus. The most recent review of this subject is that by Walker,<sup>11</sup> in *Lectures*

on the *Scientific Basis of Medicine*, in reference especially to the human fetus. Walker calls attention to the excellent studies by Dawes<sup>12</sup> on the fetal lamb, and the evidence of Lind and Wegelius<sup>13</sup> that the human fetal circulation is essentially similar. He proceeds from there to consider the oxygen saturation values found for both umbilical vein and umbilical artery blood in the human. Assuming reasonable mean values, Walker concludes that the minimal "safe" oxygen pressure in carotid blood, which on the basis of Dawes'<sup>12</sup> work he equates with umbilical artery blood, is about 15 mm. Hg and that the normal pressure is between 18 and 24 mm. Hg. The observation by Sjöstedt, Rooth, and Caligara<sup>14</sup> of a  $pO_2$  of 10 mm. Hg in amniotic fluid is consistent with this.

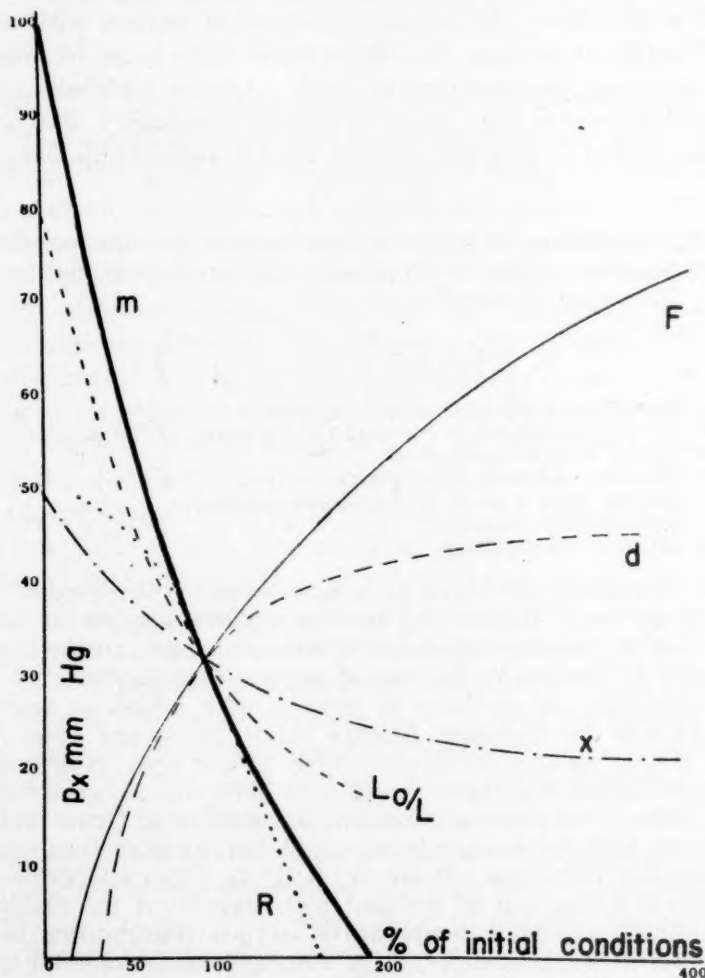


Fig. 1.—This graphic representation of the variables in the Krogh-Erlang equation demonstrates that as the intercapillary distance ( $R$ ) increases, there is a very rapid fall in the oxygen pressure ( $p_x$ ) in the tissues. There is a similar relationship of  $p_x$  with oxygen consumption ( $m$ ) and the capillary length ( $Lo/L$ ). (From Kety: *Federation Proc.* 16: 669, 1957.)

It is worthwhile to consider for a moment the meaning of the scatter of values for oxygen saturation of umbilical blood, a scatter which has been repeatedly observed (Fig. 2). For one thing, oxygen saturation as ordinarily used is the ratio of two determined values, the oxygen content and the oxygen capacity, and it therefore contains the laboratory error of both. Even if it is determined by a spectrophotometric method, the inherent error of the method



is still large.<sup>15</sup> For another, interference with delivery of oxygen to the placenta will reflect itself variably in the umbilical blood depending on fetal responses to hypoxic stimuli, so that such events as maternal anesthesia, placental separation, and volume changes related to membrane rupture will have effects varying rapidly with time.<sup>16</sup> Finally, interference with fetal placental circulation such as cord obstruction or fetal bradycardia may be expected to have still other consequences.

James and his colleagues<sup>16</sup> have discussed these factors in some detail and come to the conclusion that the values based on umbilical artery blood are of much greater value than those based on umbilical vein blood. The greater variability of oxygen saturation in umbilical vein blood is in part a consequence of the conditions under which the blood is obtained, but also of the fact that, with the same percentage error, the scatter of values in a ratio will be greater if the numerator (the oxygen content) is larger, as it is in the umbilical vein. To use the umbilical artery values alone, however, is as limited as studying renal function on the basis of renal vein blood only. We should continue to study both umbilical vein and umbilical artery blood, but in addition specify in considerable detail the conditions under which it was obtained.

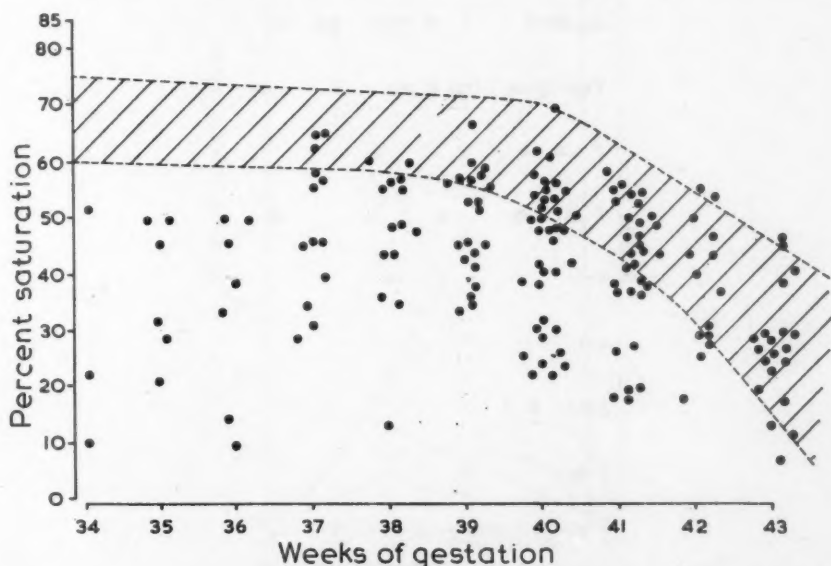


Fig. 2.—This figure demonstrates the oxygen saturation in the umbilical vein blood at birth of the human fetus. The hatched area includes all "normal" pregnancies. The great scattering of values is evident. (From Dawes: *Lectures on the Scientific Basis of Medicine*, London, 1957, Athlone Press.)

The difference between Walker's estimate of normal carotid oxygen pressure (18-24 mm. Hg) and his estimated minimal normal value (15 mm. Hg) is rather small. Indeed, he has argued for several years<sup>11, 17, 18</sup> that the human fetus is frequently subjected to conditions of chronic hypoxia, especially in postmature pregnancy in the older primigravida. The evidence for this may be considered under three headings: the oxygen capacity of the blood, the relative proportion of hemoglobin F and hemoglobin A, and the oxygen saturation of the hemoglobin present in the blood of the newborn infant.

Walker has maintained that hypoxia acts as a hemopoietic stimulus on the fetus, as it does on the adult, and that, since he found postmature fetuses to have elevated hemoglobin concentration, they had been subjected to hypoxia. That hypoxia can stimulate hemopoiesis has been strongly suggested for the

fetal lamb,<sup>19</sup> although the evidence is such that it appears unlikely that the hemoglobin concentration of the *normal* fetus is determined by hypoxia. However, Minkowski,<sup>20, 21</sup> Marks,<sup>22</sup> MacKay,<sup>23</sup> Rooth and Sjöstedt,<sup>24</sup> Prystowsky and Eastman,<sup>25</sup> and Bancroft-Livingston and Fisher<sup>26</sup> have not been able to demonstrate a rise in hemoglobin concentration past term.

Cook and associates<sup>27</sup> have corroborated the observations of Walker and Turnbull,<sup>28</sup> Cottom,<sup>29</sup> and Abrahamov, Salzberger, and Bromberg<sup>30</sup> that the proportion of hemoglobin F decreases as the fetus reaches term. They were not, however, able to substantiate Walker and Turnbull's<sup>28</sup> finding that the post-mature fetus has a rise in hemoglobin F. Further, they present evidence that a higher hemoglobin concentration in the hypoxic fetus may be the result of dehydration rather than an increase in hemoglobin mass. Bancroft-Livingston and Neill<sup>31</sup> found no significant correlation of hemoglobin F with fetal age past term.

In regard to oxygen saturation, Walker,<sup>18</sup> MacKay,<sup>23</sup> and Turnbull and Baird<sup>32</sup> have found a distinct relationship between increasing age of the mother,

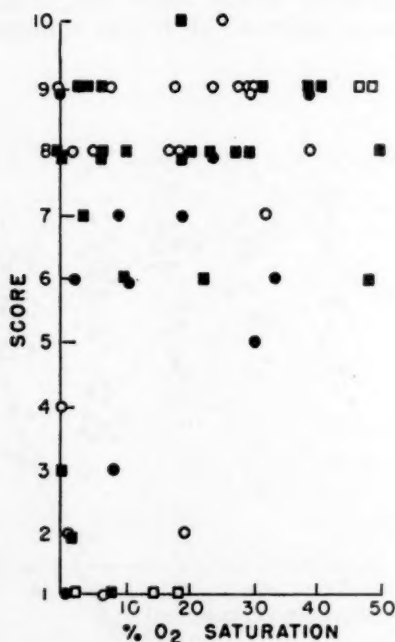


Fig. 3.—The great variability in the relationship between oxygen saturation and the Apgar score of the newborn infant is well illustrated here. ○ Vaginal delivery with regional anesthesia; ● vaginal delivery with inhalation anesthesia; ■ cesarean section with regional anesthesia; □ cesarean section with inhalation anesthesia. Note that all infants with a score below 5 have a saturation below 20 per cent, but that the converse does not hold. (From James et al.: J. Pediat. 52: 382, 1958.)

increasing length of gestation, and decreasing oxygen saturation. This is in accordance with earlier experiments by Bancroft and Young<sup>33</sup> on oxygen saturation in the blood of fetal rabbits rendered artificially postmature. No such naturally occurring condition has been observed in experimental animals, however. Furthermore, the very best work on this matter, done by Rooth and Sjöstedt<sup>34</sup> and MacKinney and co-workers<sup>35</sup> has failed to demonstrate any relationship between duration of pregnancy and parity and oxygen saturation. Bancroft-Livingston and Neill<sup>36</sup> were unable to demonstrate a change in the oxygen content of umbilical venous blood with increasing fetal age.

In this connection, the observations of James and associates<sup>16</sup> on the asphyxiated human fetus are germane. They found no significant correlation

between neonatal distress and umbilical artery oxygen content (Fig. 3), although there was a correlation with decreased pH and decreased buffer base. On the other hand, other workers have experimentally produced depression of fetal oxygen saturation along with depression of fetal pH but without clinical evidence of neonatal distress.<sup>37</sup> Finally, the oxygen saturation of the blood of the fetus of the diabetic is reduced<sup>38</sup> but there is no relationship between this and neonatal distress and no other evidence of fetal hypoxia.<sup>39</sup>

What is the explanation of these apparent inconsistencies? Part of the explanation, in all likelihood, is the difficulty of obtaining fetal blood samples under standardized conditions. But in larger measure it is likely to be that

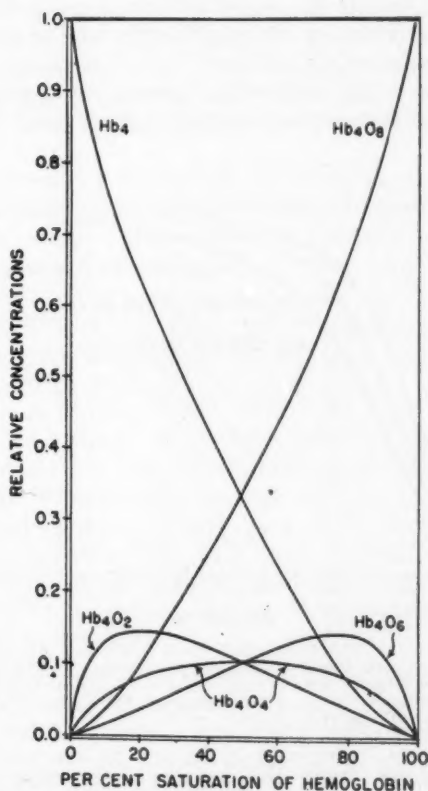


Fig. 4.—These curves illustrate the reactions involved in the combination of hemoglobin with oxygen. The dissociation curves in Fig. 5 are a composite of these. Note that at low concentrations the relationships are quite complex. (By permission from *Principles of Biochemistry*, by White et al. Copyright 1954, McGraw-Hill Book Company, Inc.)

we have, in discussing oxygen saturation, been discussing an improper measure of oxygen. As can be seen in the Krogh-Erlang equation above, it is the oxygen tension which is of importance. Further, the pressure is related to saturation by a series of parametric variables *all* of which must be known for oxygen saturation to have more than a roughly approximate significance.

Hemoglobin combines with oxygen in not one but in a series of four reactions,<sup>40</sup> the importance of each depending on the oxygen tension (Fig. 4). At ordinary adult  $pO_2$ , only the fourth reaction ( $Hb_4O_6 + O_2 \rightarrow Hb_4O_8$ ), is of significance. Although it is the interplay of these four reactions which determines the familiar shape of the oxygen dissociation curve, they have not as yet been evaluated for fetal blood, and for practical purposes the shape of the fetal curve for very low pressures is not known.

An even more important parameter is the effect of oxygenation on the strength of hemoglobin as an acid. Since oxyhemoglobin is a stronger acid than hemoglobin, it follows that any factor which decreases pH will simultaneously cause hemoglobin to have a lower oxygen affinity without change in  $pO_2$ . The commonest such factor physiologically is an increase in  $pCO_2$ . Conversely, as oxyhemoglobin loses oxygen, its capacity to bind  $CO_2$  as carbaminohemoglobin and the conversion of  $CO_2$  to bicarbonate are both increased. These relationships, known as the Bohr effect (Fig. 5), are the basis of the ability of hemoglobin to buffer the blood. The recent observation that changes in  $pCO_2$  cause changes in the shape of the red cell,<sup>41</sup> markedly altering its shape and hence the area available for diffusion may also be of physiologic importance. It follows from a knowledge of the Bohr effect that  $pO_2$  cannot be derived from oxygen saturation unless at least pH and  $pCO_2$  are known as well. Although these relationships have been determined for adult blood, they have never been evaluated for fetal blood. Manwell<sup>42</sup> has recently suggested an excellent equation for summarizing the Bohr effect, which differs from the blood of one vertebrate to another.

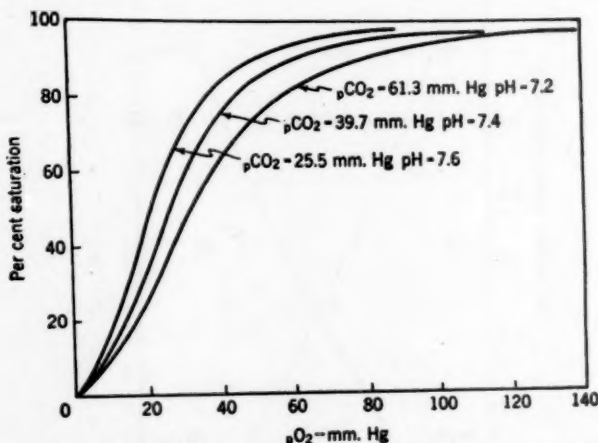


Fig. 5.—These three curves illustrate the Bohr effect. As  $pCO_2$  increases or pH decreases, the oxygen saturation at fixed pressure decreases. This effect is most striking in the steep portion of the curve—between 70 per cent and 10 per cent saturation, where most fetal values fall. (By permission from *Principles of Biochemistry*, by White et al. Copyright 1954, McGraw-Hill Book Company, Inc.)

Another problem arises from the known difference in oxygen affinity between adult and fetal blood. While, after the evidence of Allen and co-workers<sup>43</sup> is considered, it is not clear whether this is due to the ionic environment of the fetal red cell or to something in the cell stroma, there can be no doubt that the difference exists. However, from one infant to another the proportion of fetal hemoglobin varies greatly, and consequently in a series of blood specimens, at a given  $pO_2$ , a variety of oxygen saturations may be observed. Leibson and associates<sup>44</sup> were the first to observe differences in the shapes of oxygen dissociation curves from one human fetus to another. They resolved the problem by correcting their data. Unfortunately, there has not yet been a critical study of the dissociation curve of a fetal blood known to consist entirely of fetal hemoglobin, so that it cannot be decided whether this variability is due entirely to varying Hgb. F/Hgb. A ratios or not. In any event, translation from oxygen saturation values to  $pO_2$  from a single standard curve for fetal blood, without a knowledge of Hgb. F/Hgb. A relationships<sup>45</sup> cannot be considered as anything other than an approximation. Further, since McCarthy<sup>46</sup> has shown that hemolysis may reverse the relationships of adult



and fetal blood in oxygen affinity, it is of the greatest importance in laboratory studies that hemolysis be rigidly excluded in the determination of oxygen dissociation curves.

The curious observation by Meldrum and Roughton<sup>47</sup> early in their studies that carbonic anhydrase is absent from fetal red blood cells has never been fitted into the story of the movement of respiratory gases in the fetus. The presence of CAH is evidently necessary in the respiring mammal to allow the discharge of  $\text{CO}_2$  to proceed to completion in the brief passage of the red cell through the lung. In the entirely aqueous system of the placenta this may not be essential. However, the absence of CAH raises the possibility that, in vivo, there is not sufficient time for  $\text{CO}_2$  release to be completed as the fetal red cell traverses the placenta. In the laboratory, in vitro, we not only allow the reactions to be completed, of necessity, since we cannot complete our determinations before this has occurred, but actually make efforts to achieve equilibrium conditions. In vitro conditions may, therefore, differ considerably from those in vivo, especially in regard to the Bohr effect; there are literally no data on this subject.

The last major area in which we are lacking data specifically applicable to fetal blood is that concerned with the effect of temperature. As temperature drops, oxygen affinity, oxygen and carbon dioxide solubility, and pH all change.<sup>48</sup> At present we have no information about these effects in fetal blood, and the laboratory worker must either work at normal body temperature or he must employ correction factors which may not be applicable to fetal blood.

Under physiologic conditions, of course, fetal temperature is constant, and CAH and Hgb. F/Hgb. A change only very slowly, so that in vivo, in a given fetus, these factors can be put aside. But pH and  $\text{pCO}_2$  and  $\text{pO}_2$  undergo a constant cycle of rapid change as blood proceeds from the placenta (or lung) to the tissues. In the tissues, pH drops and  $\text{pCO}_2$  rises, thereby decreasing the oxygen affinity of the hemoglobin so that with a given drop in  $\text{pO}_2$  there is greater oxygen unloading than if pH and  $\text{pCO}_2$  were unaltered. Conversely, at a given  $\text{pO}_2$ , oxygen saturation will vary inversely with  $\text{pCO}_2$  and directly with pH. Consequently, no single oxyhemoglobin dissociation curve can properly be used to deduce  $\text{pO}_2$  values for blood specimens obtained from different sites or under different conditions.<sup>49</sup>

Why, in view of all these problems, have our data in the past 25 years been obtained in terms of oxygen saturation rather than oxygen pressure? The answer is a purely technical one. Until the end of World War II, gasometric techniques required the use of prohibitively large quantities of blood, and other methods were not sufficiently accurate.<sup>50</sup> Oxygen tension could be determined only by measuring oxygen content and oxygen capacity and then establishing, by equilibration of additional samples with known gas mixtures, a dissociation curve with which the actual sample could be compared. A group of correction factors for pH,  $\text{pCO}_2$  and temperature were experimentally determined for adult blood and these are still used in work on fetal blood,<sup>51</sup> although there is no evidence of their validity. Whenever the quantity of blood was limited, a dissociation curve could not be prepared, and approximations had to be made from saturation values.

The introduction of the Riley bubble method at the end of the war,<sup>52</sup> using about 1 ml. of blood and equilibrating it with tiny bubbles of known gas mixtures, promised an end of this problem. The method has been used in fetal studies.<sup>18, 53, 54</sup> However, it has emerged<sup>55</sup> that the method has an increasing error at partial pressures of oxygen below about 50 mm. Hg and indeed, in the ordinary range of fetal  $\text{pO}_2$  its error is probably as great as that of an approximation from oxygen saturation values.

We appear to be on the threshold of the necessary technical breakthrough. Molecular oxygen in an aqueous medium will induce a current in a suitable electrode, and this current is proportional to the  $pO_2$ . Measuring the current and standardizing it presents no problems, but the electrode itself has presented considerable difficulties because the oxygen tends to react with it. The best solution until recently was the constantly refreshed falling drop mercury electrode,<sup>56</sup> but this unfortunately requires relatively large amounts of blood and is difficult to use anaerobically. The recently developed Clark electrode or some variant of it,<sup>57</sup> such as a permanent electrode sealed with a membrane, may solve these difficulties and make practical for the first time the rapid direct determination of  $pO_2$  at low partial pressures in biologic fluids. Sjöstedt, Rooth, and Caligara<sup>14</sup> have already reported on the  $pO_2$  of amniotic fluid by this technique and are at work on the  $pO_2$  of umbilical blood.

It is very likely that we shall have to wait until a reasonable amount of data has been gathered before we can determine the normal fetal  $pO_2$ . Only then can we give a definition of hypoxia which will be physiologically and experimentally meaningful. The sooner we begin to state our values in terms of oxygen tension, the sooner we shall be able to present verifiable quantitative answers concerning the role of oxygen deprivation, acute and chronic, in the etiology of fetal morbidity.

In tribute to the many dedicated workers in this difficult field, lest it be felt that disparagement of their contributions has been intended, attention may be called to Benjamin Franklin's<sup>58</sup> remark concerning his explanation of the superiority of pointed conductors:

"I have at present nothing better to offer in their stead, I do not cross them out: for even a bad solution read, and its faults discovered, has often given rise to a good one, in the mind of an ingenious reader."

*Addendum.*—Attention should be directed to the paper by Sjöstedt, Engleson, and Rooth<sup>60</sup> for a detailed discussion of what they designate as "dysmaturity." They report decreased oxyhemoglobin saturation and increased hemoglobin concentration in the presence of dysmaturity, findings which are the same as Walker's in prolonged pregnancy.

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## A CONTRIBUTION TO THE STUDY OF VARICOSE VEINS IN PREGNANCY

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VARICOSE veins are often observed during prenatal examinations. Our patients with large varices during pregnancy have noted a feeling of fatigue in the lower extremities that seems to be progressive throughout pregnancy, with considerable relief at delivery. Some patients, however, describe acute pain in certain parts of the legs, which is usually associated with specific areas in the venous system. On examination these areas feel warm and are surrounded by cooler skin, a difference in temperature that can be detected by gross palpation. Such areas are usually surrounded by small venules often radiating from a central focus and resembling, on a larger scale, the vascular spiders of pregnancy (Figs. 1 and 2). Fried, Perilstein, and Wagner<sup>1</sup> called these areas angiectids. We have noted, as have they, that these warm, tender varicosities are most painful when the patient assumes the erect position. They cause the greatest discomfort during the middle trimester of pregnancy, rarely being felt in the first trimester and becoming somewhat less uncomfortable during the last trimester. So sharply localized is the pain that the patient can put her finger over the varix causing the maximum tenderness. These varices are no longer warm or tender after delivery but they recur during subsequent pregnancies. In a number of women who had these "hot" varices (as we have called them) during several pregnancies, the same manifestations that were noted in the middle trimester of a pregnancy also occurred during the premenstrual period. The acute symptoms, however, disappeared with the onset of menstruation.

These varicosities seem to be physiologically different from the ordinary saphenous varix. Since it was thought that they might be arteriovenous fistulas in the lower extremities of pregnant women, we decided to study them from the point of view of oxygen saturation. Accordingly, oxygen saturation values were secured on blood drawn from the varix itself and from venous blood from the other or upper extremity for comparison with oxygen saturation values of arterial blood from the pulmonary laboratory at Ochsner Foundation Hospital.

A number of these patients (Table I) had increased oxygen content in the blood of the "hot" varix. This indicates that a communication of considerable size with the local artery must be present. The relationship of oxygen



saturation to the period of gestation is shown in Fig. 3. A review of the American medical literature indicates that such determinations have not been made on pregnant women with varicose veins who have been studied. Piulachs and associates,<sup>2</sup> however, in their studies of varicose veins, concluded that there are arteriovenous fistulas in the lower extremities of pregnant women communicating with varicose veins. They believed that such fistulas are the predecessors of varicose veins in the saphenous system. They noted that oxygen saturation values were 2 to 7 volumes per cent higher in the extremity with these abnormal varicose veins and believed that the arteriovenous fistula tends to close after delivery. Arteriography, in their hands, revealed that the dye moved from the arterial system into the venous system more rapidly than



Fig. 1.—Varicosities of the lower extremity that are warm and tender. These appear to be intracutaneous arteriovenous fistulas.

it did in limbs in which there were no varices. Piulachs and Vidal-Barraquer<sup>3</sup> considered progesterone and the posterior pituitary hormone as playing a fundamental etiological role. Other authors<sup>4-6</sup> thought that a hormonal influence is the cause of varicose veins in pregnancy. McCausland<sup>4</sup> believed that

progesterone is the principal factor in causing dilatation of the venous walls, just as the ureter and gastrointestinal tract are relaxed in pregnant women. He noted that there seems to be a low incidence of abortion in women with varicose veins. He and Marazita<sup>5</sup> used the estrogenic hormone, Progynon-B or Ovocylin dipropionate in the treatment of varicose veins in pregnancy with complete relief of symptoms in approximately 50 per cent and partial relief in the remainder.



Fig. 2.—Common distribution of varicosities on the lower extremity.

In our patients who had increased oxygen saturation in the "hot" varicosity, 25 mg. of stilbestrol a day relieved symptoms (Fig. 4) but discontinuance of use of this drug caused recurrence of symptoms and increase in oxygen saturation. It is of interest to note that patients who have "hot" varicosities with symptoms prior to their menstrual period also show increased oxygen saturation at this time in contrast to the oxygen saturation during the intermenstrual period (Fig. 5). They likewise are relieved of symptoms by taking stilbestrol immediately before the onset of menstruation and have noted recurrence of symptoms in cycles when stilbestrol was not administered.

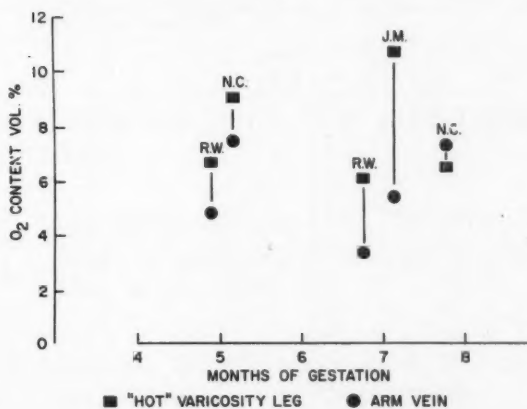


Fig. 3.—The maximum oxygen saturation of the blood of "hot" varices occurs toward the end of the middle trimester of pregnancy. Symptoms and oxygen saturation diminish at term.

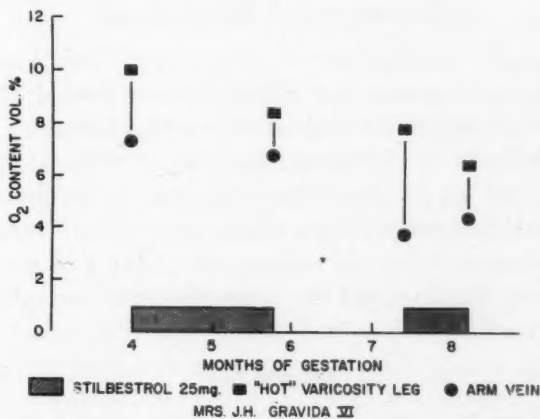


Fig. 4.—The effect of administration of stilbestrol on oxygen saturation of venous blood in "hot" varicosities.

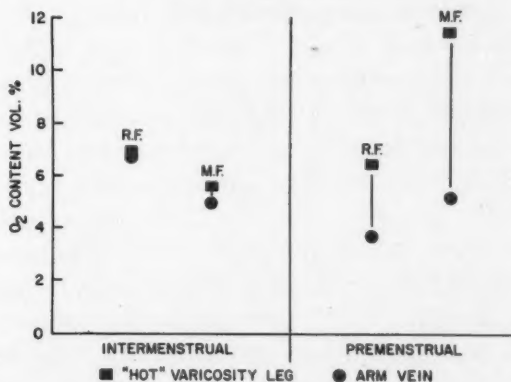


Fig. 5.—Oxygen saturation of "hot" varicosities in 2 patients in relation to the menses.

TABLE I. OXYGEN CONTENT OF PREGNANT WOMEN WITH "HOT" VARICOSITIES

CASE	OXYGEN CONTENT	
	ARM VEIN (VOL. %)	LEG VEIN (VOL. %)
1	7.2	7.8 calf 8.7 thigh
2	6.6	7.4
3	3.7	11.1
4	6.5	6.7
5	7.1	4.8
6	7.9	12.0 right knee 9.3 ankle
7	6.5	12.3
8	5.6	10.3
9	10.0	9.2
10	7.5	10.3
11	3.6	10.8
12	4.7	9.3
13	7.7	7.6
14	5.5	10.3

Standard error &lt; 2 volumes per cent.

### Summary and Conclusions

Studies on certain varicosities in pregnancy indicate that there is an arteriovenous fistula in these areas, which is manifested clinically by warm, tender angiectasis and becomes symptomatic with change of position. Oxygen saturation studies indicate a significant increase in arterial blood in these areas as contrasted with venous blood of the opposite leg or the upper extremities. Administration of stilbestrol results in improvement of symptoms. The same symptoms occur premenstrually in women who have had warm varicosities for a long time and are ameliorated by administration of stilbestrol. Further studies are in progress.

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## THE USE OF ANTICOAGULANTS FOR THROMBOPHLEBITIS DURING PREGNANCY\*

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IN 1945, Yahr, Reich, and Eggers<sup>30</sup> reported the use of anticoagulant drugs during pregnancy. This first publication was followed by isolated case reports until Adamson, Weaver, and Jaimet<sup>1</sup> in 1950 and H. P. Wright<sup>27</sup> in 1951 reported larger series.

Meanwhile experiments on animals by Quick,<sup>19</sup> and Kraus, Perlow, and Singer<sup>13</sup> had confirmed observations made in cattle with sweet clover disease. Dicumarol was shown to pass the placental barrier and produce coagulation defects in the fetus with resultant fetal death from hemorrhage in utero or soon after delivery. With lower dosages of Dicumarol which did not produce bleeding in the mother, however, the offspring survived until after delivery and, if affected, could be salvaged by the administration of vitamin K. Subsequently, considerable doubt has been raised as to the advisability of antepartum anticoagulation with coumarin derivatives and, to confirm this, the unsatisfactory results of several studies have been published.

In 1947, von Sydow<sup>23</sup> reported a case in which anticoagulants had been given just prior to delivery and extensive hemorrhagic sequelae had been noted in the infant. Subsequently, Sachs and Labate<sup>21</sup> reported one intra-uterine death due to visceral hemorrhage and, more recently, Blum<sup>4</sup> reported the same complication but without evident hemorrhage in the macerated fetus. In both of these cases, however, prothrombin times above the therapeutic range occurred prior to the time of the accidents. Wright<sup>27</sup> reported a neonatal death due to a tentorial tear and subsequent hemorrhage. In her opinion, anticoagulant therapy given to the mother just before delivery may have aggravated the hematoma.

These accidents occurred during treatment with coumarin derivatives. It is not surprising that as a result the present tendency is to use heparin during pregnancy, especially near term.<sup>2, 4, 15, 16</sup> As yet, no fetal complications have been reported with this drug and it may not pass the placental barrier.†

\*Aided by grants from the Lasker, Hampil, Hyde, and Fullerton Foundations and the National Heart Institute.

†Drugs with a molecular weight of less than 1,000 pass the placental barrier but above that weight a certain selectivity occurs.<sup>9</sup> Heparin has a molecular weight of about 20,000. Vitamin K is slowly transmitted to the fetus.<sup>20</sup>

Nevertheless, occasional cases may require long-term anticoagulant treatment during pregnancy, as, for example, patients with recurrent phlebitis with or without pulmonary emboli, and patients with rheumatic heart disease with embolization; also, in simple thrombophlebitis, where short-term therapy is indicated, recurrences and pulmonary emboli occur quite often if anticoagulant treatment is shorter than 2 weeks.<sup>3, 4, 10</sup> Management of such cases with heparin is difficult or impractical with the result that there are few reports of patients treated exclusively with this drug.

These reasons would seem enough to discourage the use of anticoagulants in pregnancy for thrombophlebitis. Serious complications and sequelae can occur if they are not used,<sup>11, 24</sup> however. The significance of embolism was well shown by Ullery<sup>22</sup> in 1954. In a review of 97 cases published previously in the literature he recorded 15 deaths from pulmonary emboli; but in 38 patients treated with anticoagulants he found that no fatal pulmonary embolism had occurred. Though these were evidently selected cases, the danger to maternal and secondarily to fetal life cannot be denied.

The problem of anticoagulant therapy in pregnancy is not one of its value in the treatment of thrombophlebitis since this has been well established in the nonpregnant state. It is concerned, more precisely, with the safety of such therapy and requires weighing the risk of thromboembolism versus the dangers of anticoagulation. Some authors<sup>14, 22, 27, 30</sup> have noted good results by using a lower therapeutic level than that they recommend for the nonpregnant patient and this may explain their low incidence of complications. These and other problems remain to be solved. It was hoped that a review of our experience in this field in conjunction with previous reports of other authors should be of assistance in devising a logical program for anticoagulant therapy in pregnancy.

### Material and Technique of Analysis

In preparation of this survey, the hospital records of 63 patients were reviewed. These records represented all the pregnant patients admitted to the Lying-In Hospital from January, 1945, to January, 1957, in whom the clinical diagnosis of thrombophlebitis was made. It was necessary to reject 6 of the records because of insufficient information to confirm the diagnosis or catalogue adequately the extent of the disease and its treatment.

Each instance of thrombophlebitis was considered as an episode and observed through an arbitrary period of 42 days from the onset of symptoms and signs. If these cleared and then recurred during the observation period, this recurrence was considered part of the original illness under the term of second phlebitis. A recurrence after this limit of time, however, was analyzed as a separate episode. Each episode was classified according to the type of treatment given, as follows:

1. Untreated: Treated with bed rest, elevation of legs, hot packs. Regional anesthesia was also used in two patients.
2. Treated: Above-mentioned measures plus anticoagulant therapy.
3. Delayed-treated: Initial treatment as in untreated group and anticoagulant therapy instituted at a later date for specific reasons.

The anticoagulant treatment was considered as starting on the day a first dose of drugs was given. While this may have been the day treatment became effective with heparin, it was not so when slower-acting anticoagulants were

used. Consequently, in these instances we provided a correction, using the actual prothrombin time to determine the beginning of effective treatment. This correction, however, was used only in the analysis of complications in the treated group. Episodes were catalogued as to type by the extent and localization of the disease on clinical examination: (a) deep phlebitis, subdivided into sural, femoral, and pelvic or iliac; (b) superficial phlebitis, subdivided into localized (less than 10 cm. long) and extensive.

The results obtained from this clinical survey may be divided into the following three categories:

1. *General Information on Antepartum Thrombophlebitis.*—

*A. Yearly and general incidence:* During a 12 year period (1945-1957), 57 patients were studied completely. The majority of the 64 episodes they suffered were noted to occur in the last 5 years with a peak of 11 in 1952 (Fig. 1). It is felt that this apparent increase over previous years represented increased interest and knowledge on the part of the physicians, availability of more specific treatment, and better follow-up in the antenatal period.

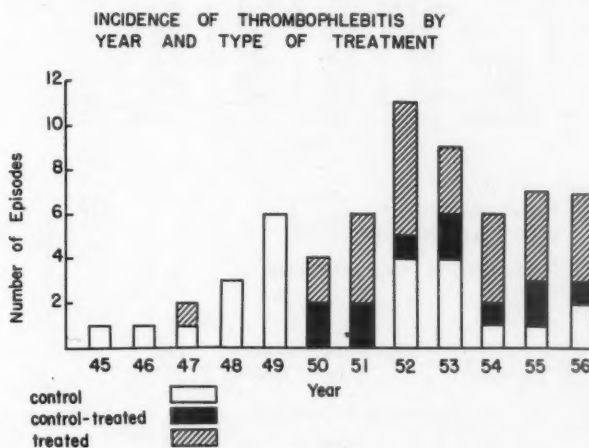


Fig. 1.

For these reasons, if we consider only cases of superficial extensive or deep phlebitis in the last 5 years, the general incidence should be more accurate. Including rejected charts where the type of phlebitis could be determined, the incidence was 0.132 per cent for both varieties and 0.079 per cent for deep phlebitis alone.

*B. Age incidence:* The age incidence in the studied cases was compared with the age distribution in 26,490 terminated pregnancies which occurred between 1947 and 1952. The results (Fig. 2) showed a definitely higher incidence in the 31 to 35 and 36 to 40 year categories.

Variations within the study group were noted according to the type of phlebitis. Deep thrombophlebitis tended to appear more frequently in the 21 to 25 year category with a slight secondary rise over 35 years of age. Superficial thrombophlebitis occurred more frequently in the 31 to 35 year group.

*C. Trimester incidence:* While no seasonal preponderance was noted, a majority of the episodes occurred in the last trimester of pregnancy (57.8 per cent). Of these, however, only 35.1 per cent happened in the last 6 weeks prior to delivery. This high incidence was even more evident with superficial phlebitis, except in primigravidas where no difference could be found between the second and third trimesters.

*D. History of varicose veins:* A past history of varicose veins was present in 49 per cent of the study group. However, 91.6 per cent of the patients with

superficial localized phlebitis had such a history compared to 30 per cent for the group with deep phlebitis (Fig. 3).

*E. Influence of parity:* Deep thrombophlebitis occurred at a somewhat lesser parity than the superficial type (Fig. 4). Eighty per cent of the deep cases had occurred during the first three pregnancies, but for the superficial variety a similar percentage was not reached until after a fourth pregnancy.

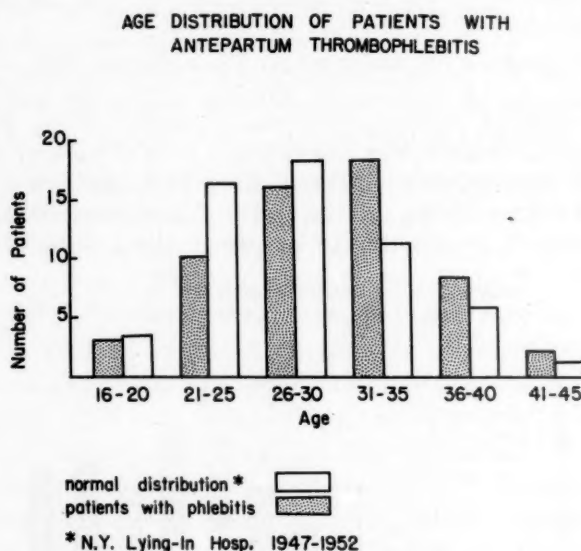


Fig. 2.

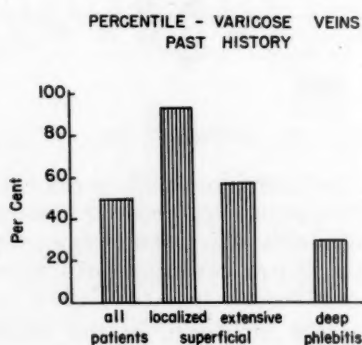


Fig. 3.

*F. Types of thrombophlebitis:* Superficial thrombophlebitis accounted for 34 of the episodes, 13 localized and 21 extensive. The remaining 30 were deep phlebitis, 16 sural, 12 femoral, and 2 iliac or pelvic.

*G. History of previous thrombophlebitis:* Of the 57 patients, 19.3 per cent presented a history of previous phlebitis. These patients had suffered a total of 19 episodes, 7 of which had occurred in relation to pregnancy.

*H. Associated diseases:* The associated diseases found in our patients were: (1) heart disease 7; (2) infection (genital, urinary, or lower limb) 4; (3) post-phlebotic syndrome 4; (4) pre-eclampsia 2; (5) iron deficiency anemia 2; (6) collagen disease (1 proved, 1 doubtful) 2; (7) recent abdominal surgery 2.

*Comment:* The Anglo-American medical literature on antepartum phlebitis gives only scanty information as to predisposing factors. Most of the articles



published limit their conclusion to the general incidence of the disease which varies from 0.018 per cent<sup>22</sup> to 0.1 per cent,<sup>26</sup> dependent partly on whether or not both deep and superficial types of thrombophlebitis were included. Our higher incidence may also be related to the fact that there are two active clinics for the treatment of venous disease in our hospital.

Donaldson<sup>7</sup> in a review of 49 cases published over a period of nearly 60 years could not give definite figures as to predisposing factors because of the lack of pertinent information in some publications. He noted a high incidence of the disease in the last trimester of pregnancy, however, and this was confirmed by others.<sup>22, 25</sup> Age was considered unimportant in his analysis as well as in that of Weiss and Turner.<sup>25</sup> In this last article parity was also thought unimportant.

## 2. Comparison Between Patients by Type of Treatment.—

To make a statistically significant comparison between treatment with or without anticoagulants a true control group would be necessary. It was felt

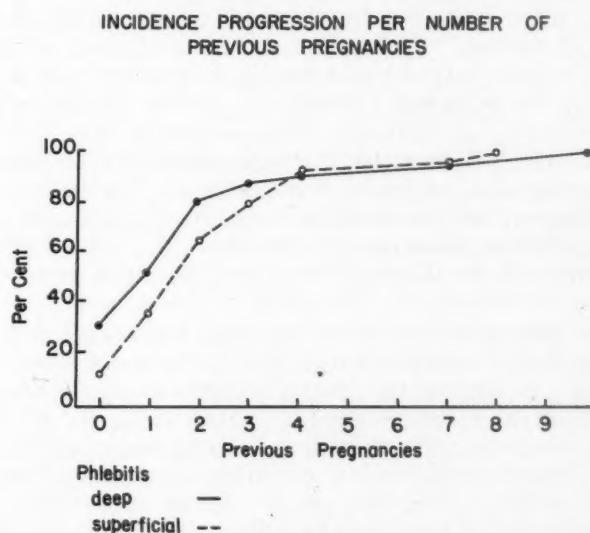


Fig. 4.

at the beginning of this study that variations in individual patients might well have influenced the choice of treatment, occurrence of complications, or outcome of pregnancy in any one case or episode. Since this is not a control-treated study, a wide difference in respect to important variables was expected and did in fact occur.

*A. Division per group:* Of the 64 episodes observed, 24 fell into the untreated group, 29 in the treated, and 11 in the delayed-treated category.

*B. Observation time:* Of 13 episodes which occurred prior to 1950, only one was treated with anticoagulants and since then 39 out of 51 belonged to this category (Fig. 1).

*C. Type of thrombophlebitis:* Deep phlebitis was more frequently treated with anticoagulants than the superficial variety (20 treated cases against 5 untreated and 5 delayed-treated).

*D. Fetal wastage:* The treated group showed a higher incidence of previous spontaneous abortions, excluding therapeutic and criminal (7 patients with a total of nine abortions against 4 with a total of five abortions in the untreated group). Three patients had a past history of deadborn infants; 2 of these were untreated patients and the third a treated patient.

*E. Previous thrombophlebitis:* Eight treated patients had a past history of 16 phlebotic episodes versus 2 patients with a total of 2 episodes in the untreated group.

Other factors such as age, parity, and previous hemorrhage were analyzed and showed no important differences.

*Comment:* Such wide discrepancies between patients subjected to different forms of treatment preclude any direct comparison of the results. Important factors like a previous tendency to venous thrombosis and fetal wastage as well as the type of thrombophlebitis can doubtless modify the incidence of thromboembolic accidents and fetal loss. A survey of these complications, however, using the terms untreated and treated for identification only, may help in an evaluation of treatment for antepartum thrombophlebitis.

### 3. Complications per Therapy Groups.—

*A. Anticoagulant therapy:* Before complications are discussed, the program of anticoagulant therapy should be reviewed.

Anticoagulants were managed by the staff or attending obstetrician while the patient was hospitalized. If treatment was continued after discharge the Anticoagulant Clinic took over. Prothrombin determinations were done in the first case by the hospital's Central Laboratory, and in the second, by the Vascular Research Laboratory. A different thromboplastin was utilized in the two laboratories despite which a level of 25 to 39 second<sup>29</sup> was generally accepted as the optimum therapeutic range for reports from either laboratory.\* In this clinic, excessive effect of anticoagulants, even in the absence of pathological bleeding, was controlled as soon as reported with the use of small amounts of vitamin K<sub>1</sub> by mouth (5 to 10 mg.), and readjustment of the dosage of the drug.<sup>8</sup>

A total of 33 patients were treated with anticoagulants ante partum. Thirty of these received treatment on a short-term basis from one to 60 days with a mean duration of 15.3 days. Subdivision was as follows: 1-7 days, 11; 8-14 days, 8; 15-21 days, 5; 22-28 days, 0; 28-39 days, 5; 60 days, 1. Three patients were placed on long-term anticoagulants because of a history of recurrent thrombophlebitis. The mean duration of therapy ante partum for this group was 164.7 days.

Several combinations of anticoagulant drugs were employed as follows:

#### *Single Drug.—*

Dicumarol	14
Marcumar	2
Tromexan	5

#### *Combination.—*

Heparin-Dicumarol	5
Heparin-Tromexan-Dicumarol	2
Heparin-Tromexan-Marcumar	1
Tromexan-Dicumarol	6
Tromexan-Marcumar-Dicumarol	1

The duration of short-term treatment varied widely, as noted. In 2 patients it was decidedly too short (one week) and a second episode of thrombophlebitis developed within one week of abrupt cessation of therapy. The patients treated on a long-term basis uniformly required larger than average doses of anticoagulants to maintain therapeutic levels. Even with these large doses their prothrombin time frequently dipped below the therapeutic range. This group had previously accumulated a total of 12 phlebotic episodes and may be referred to as "clotters"; herein lay the indication for long-term therapy.

\*Link and Shapiro's modification of the Quick one-stage prothrombin time.

Importance is attached to the fact that slow-acting drugs alone were used in 14 of 36 treated episodes and heparin was not utilized in 27. It will later be shown that the use of faster-acting agents might have prevented some early complications.

*B. Thromboembolic complications:* On conservative management 7 patients developed the following 8 complications: extension of deep phlebitis, 3; extension of superficial phlebitis, 4; pulmonary embolus, 1 (Case 4, Table I). Of these 7 patients, 6 were placed on anticoagulant therapy and considered as treated thereafter.

TABLE I. EVIDENCE FOR PULMONARY EMBOLI

CASE	CHEST PAIN	COUGH	HEMOPTYSIS	ECG	X-RAY	TEMP.	PULSE	SEVERITY
<i>Treated Group.—</i>								
1	+	0	0	Not done	Neg.	+37.8	+96	+
2	+	0	0	Suggestive	Neg.	+38.2	+106	+
3	+	+	+	Suggestive	Neg.	37.0	+92	++
<i>Control Group.—</i>								
4	+	+	+	Neg. RHD	Review positive	+37.2	+106	+++

Five patients who received anticoagulant therapy developed the following 6 complications: extension of deep phlebitis, 1; pulmonary embolus, 3 (2 of these inconclusive) (Cases 1, 2, and 3, Table I); secondary phlebitis, 2. As can be seen in Table II, 3 of these complications occurred after treatment had been abruptly discontinued and the prothrombin time had returned to below therapeutic level (Cases 4 and 5, Table II). In examining the remaining complications we find evidence that inadequate prothrombin levels were present in Case 1 at the time of the occurrence. Case 2 had been treated with Dicumarol alone for only 2 days when she presented the same complication; therapeutic levels had just barely been reached. In both of these last instances, however, the evidence for pulmonary emboli was not conclusive (Cases 1 and 2, Table I). Case 3 had been treated initially with conservative measures plus continuous caudal anesthesia. Four days after the onset of Dicumarol therapy extension of the disease was noted in the chart. It was impossible to ascertain whether this had occurred prior to effective anticoagulant therapy or not.

Consideration of the delayed-treated group discloses additional facts. Six of these patients did not receive anticoagulant therapy initially because they were near term when the phlebitis occurred. In one, the disease extended and in another a severe pulmonary embolus made anticoagulation mandatory. She was delivered under full treatment without complications (Case 4, Table I). The remaining 5 patients were treated post partum only. Four more patients were managed with conservative measures at first for no particular reason. Three developed an extension of the disease and the fourth had persistent symptoms after 2 weeks of this therapy. All 4 were subsequently placed on anticoagulants. Finally, a last patient received this treatment after some delay because of an uncertain diagnosis on admission.

Recurrences during the same pregnancy occurred in 7 patients. Four of these were not under anticoagulant treatment at the time. All three "clotters" had recurrences. In one, however, treatment had been stopped 3 days before because delivery was imminent and in another the prothrombin level was well below the therapeutic range.

*Comment:* Should we eliminate from the treated group the patients in whom thromboembolic complications occurred before effective treatment was established, a considerable differential between untreated and treated groups

would be evident. The actual differential although small is rather important in view of the previously mentioned fact that the majority of the treated cases were of greater severity. It seems likely that with the use of the more rapidly acting anticoagulants, longer treatment as indicated, and gradual reduction of dosage before stopping, fewer complications would have occurred. This last assertion is based on recent work by Carter and colleagues<sup>5</sup> from this laboratory, which seems to indicate that abrupt cessation of therapy may enhance the recurrence rate of thromboembolism.

TABLE II. THROMBOEMBOLIC COMPLICATIONS IN THE TREATED GROUP

CASE	COMPLICATION	DRUG IN USE	NO. DAYS AFTER FIRST DOSE	NO. DAYS' EFFECTIVE TREATMENT	PROTHROMBIN TIME
1	Pulmonary embolus? (Case 1, Table I)	Tromexan	2	0	14.6
2	Pulmonary embolus? (Case 2, Table I)	Dicumarol	2	1	26.9
3	Extension of a deep thrombophlebitis	Dicumarol	4	2	30.7
4	Secondary superficial	Dicumarol	Stopped 6 days before		17.8-14.5
5	Secondary deep	Dicumarol	Stopped 3 days before		12.8
5	Pulmonary embolus (Case 3, Table I)	Mareumar	Stopped 3 days before		17.0

Withholding anticoagulant therapy when phlebitis occurs near term does not seem justified in view of the complications noted in 2 of our patients in this situation. The related problem of anticoagulation at the onset of labor and delivery, which disturbs the clinician, will be discussed shortly (Section F).

The rate of recurrence of various phlebitic complications in the same pregnancy after a first episode seems very high. From the total, however, should be removed the patients who were habitual "clotters." Anticoagulants in these patients are sometimes ineffective and they are prone to develop complications despite therapy. Nevertheless, every effort should be made to reduce their number and severity.

Our criteria for pulmonary embolism should be reviewed. In any case, lack of evidence from the ECG or chest x-ray cannot be considered as eliminating its possibility. Patients without a previous history of pulmonary congestion may suffer no infarction from the embolus, depending on its size.<sup>12</sup> X-ray findings and electrocardiographic evidence may be found only with serial recordings. In their absence, greater importance was attached to the clinical picture, i.e., pleuritic pain, cough, hemoptysis, etc., in making the diagnosis. In 2 of our patients, the absence of some of these characteristics made the diagnosis doubtful. If we accept these, however, the general incidence of pulmonary embolus per episode was 6.3 per cent and, including the rejected charts, 7.2 per cent. This is below the percentage found by Ullery,<sup>22</sup> probably because his was calculated from inadvertently selected cases, but it disproves the contention that antepartum thrombophlebitis is rarely complicated by pulmonary embolus.<sup>1, 6</sup>

Besides this serious threat to life, the disabling long-term complications which may result from the phlebitic process must also be considered. Extension of the disease will produce proportionately more valvular defects and chronic venous insufficiency. For these reasons, promptly effective treatment



seems advisable as soon as the diagnosis is made, provided that maternal and fetal hemorrhagic complications can be minimized. Whether or not cases of localized superficial phlebitis should be treated with anticoagulants depends on its localization and tendency to progression.

*C. Hemorrhagic complications:* Under conservative therapy 3 hemorrhagic complications occurred—one premature separation of the placenta, followed by premature delivery of a living infant, one gastrointestinal hemorrhage due to peptic ulcer, and one case of epistaxis.

Under anticoagulant treatment during the observation period, 6 patients in 40 treated episodes had a total of 7 hemorrhagic complications (Table III).

TABLE III. HEMORRHAGIC COMPLICATIONS IN THE TREATED GROUP

CASE	COMPLICATION	UNDER TREATMENT	THERAPY FOR COMPLICATION	OUTCOME	HIGHEST PROTHROMBIN TIME (SECONDS)
1	Postpartum bleeding	Yes	None	—	27.3
1	Nose bleed	Yes	Vitamin K <sub>1</sub> plus local treatment	—	31.6
2	Nose bleed	Yes	Local treatment	—	37.3
3	Abortion	No	None	Abortion due to operation	51.0
4	Large intervillous hematoma	Yes?	None	Fetal death	40.9
5	Threatened abortion	No	None	Normal full-term	22.3
6	Postpartum hemorrhage	Yes	Transfusion with Vitamin K <sub>1</sub>	—	23.6

Two of these were epistaxis controlled by local treatment and in one case by vitamin K (Cases 1 and 2). One abortion occurred after direct surgery on an unsuspected pregnant uterus after the patient had been on prophylactic anticoagulant therapy because of previous thrombophlebitis (Case 3). In one case which will be discussed later in detail, a large intervillous hematoma was found in the placenta at the delivery of a dead infant (Case 4). A fifth patient developed threatened abortion after cessation of therapy but the symptoms subsided and she was delivered at term of a normal infant with a normal placenta (Case 5). Finally, 2 instances of postpartum bleeding occurred—one very slight 10 days post partum due to retained membranes (Case 1), the other 5 days post partum, severe, requiring transfusions and vitamin K (Case 6). In this last case no curettage was performed to see if retained secundines were the cause; however, manual removal of the placenta had been done at delivery.

*Comment:* In none of these cases could coumarin toxicity, as evidenced from the highest prothrombin time reached, be demonstrated. One possible exception was the patient (Case 3) in whom abortion occurred, although, as mentioned, surgery alone could explain this complication. Local causes were responsible in the others for the initiation of bleeding except in Case 4 which will be discussed later and in Case 6 where there is some doubt as to the actual etiology. Only this last complication was severe enough to require transfusions and cessation of anticoagulant therapy, which, however, had not yet reached therapeutic levels. We are inclined to believe that anticoagulants did not initiate the bleeding in this case, but may have aggravated it.

*D. Fetal outcome:* There were no maternal deaths in this series. Fetal deaths occurred in the treated group, however, and merit careful analysis.

In 33 patients treated with anticoagulants ante partum there were 2 abortions and 3 intrauterine deaths. One anomalous infant was also delivered.

The abortions appeared to have had little relationship to anticoagulant therapy. The first, at 6 weeks, followed direct trauma to the uterus at abdominal operation. The second was a therapeutic abortion indicated by the development of a psychosis. In the latter case abortion was performed 8 days after cessation of Tromexan therapy. Despite the fact that the prothrombin time had reached 100 seconds on one occasion, both fetus and placenta were normal, an observation which can be compared to those of Merz and Breitner<sup>16</sup> in patients who received anticoagulants in high dosage for short periods of time, before therapeutic abortions. The intrauterine deaths are described in Table IV. In all 3 cases the fetal heartbeat was lost and fetal movements ceased while the patient was receiving anticoagulants. In none of these instances did the prothrombin time rise above 45 seconds. The drugs involved were Dicumarol and Tromexan.

TABLE IV. INTRAUTERINE DEATHS ON ANTICOAGULANTS

CASE	TIME OF FETAL DEATH	TYPE AND LENGTH OF TREATMENT	HIGHEST PRO-THROMBIN	FETUS	PLACENTA	PREVIOUS FETAL WASTAGE
1	30 weeks	Dicumarol 1,400 mg./13 days	44.6	Macerated. Some organs stained by hemoglobin	Normal	Gravida ii, no wastage
2	23 weeks	Dicumarol 1,850 mg. } Tromexan 16 } 2,400 mg. } days	33.5	Macerated	Normal	Gravida v, 1 abortion
3	36 weeks	Dicumarol 4,150 mg. } Tromexan 35 } 1,200 mg. } days	40.9	Macerated	Red infarct, intervillous hemotoma	Gravida x, 2 abortions, 1 deadborn

Pathological examination of the fetus was obtained in each case. All 3 were macerated and had been delivered up to four months after death. There were no significant gross findings except in Case 1 where some organs were noted to be stained with hemoglobin. Examination of the placenta was normal except in Case 3. Here, a red infarct was noted which on microscopic examination proved to be a large intervillous hematoma.

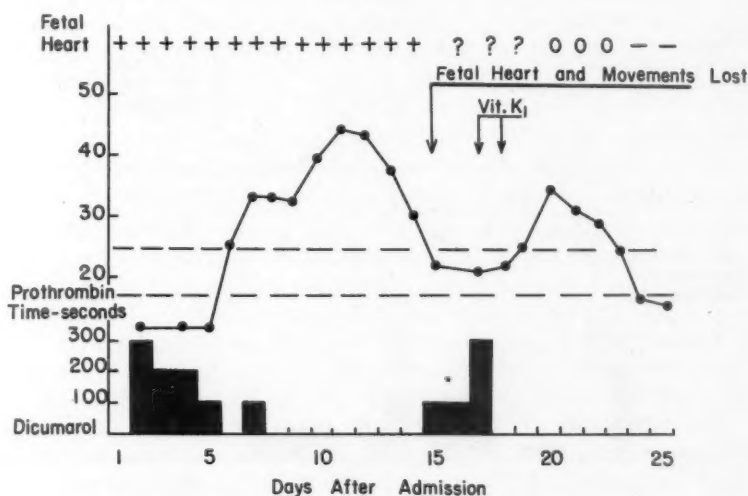
A detailed review of Case 3 discloses other significant facts. This patient was a gravida x with a previous history of 2 spontaneous abortions and one intrauterine death. Three weeks prior to death of the fetus she developed severe acidosis secondary to prolonged vomiting. This patient required large doses of anticoagulants to maintain therapeutic levels and her prothrombin time determinations were somewhat erratic. While there is no definite evidence for erroneous reports they are a possibility. The intervillous hematoma could be of significance but it is not an unusual finding and not necessarily indicative of hemorrhagic disease.

Our conclusions regarding this patient were that multiple factors could well have contributed to fetal death. Anticoagulant therapy cannot be eliminated as a possible cause but the factors of poor obstetrical history and recent severe acidosis seem equally if not more significant.

The remaining cases of intrauterine death have no explanation other than anticoagulant therapy or spontaneous coincidental death. The previous abortion in Case 2 does not seem of significance here. In neither case was an excessively high prothrombin time recorded although in Case 1 reports slightly above therapeutic range were obtained. Of considerable interest is the fact that both fetal deaths have occurred in association with a peak level of hypoprothrombinemia (Figs. 5 and 6). This suggests an association with anticoagulant therapy.

Both of these deaths occurred during a 3 month period in 1954 and review of the records discloses that rather large doses of drugs were used in both cases. The laboratory reporting the prothrombin determinations at the time was using a different thromboplastin from that employed in our research laboratory. Comparisons on identical blood samples had shown a marked

CASE NO. 1



Interrupted lines indicate corrected therapeutic range

Fig. 5.

difference in the results suggesting that the thromboplastin in use was relatively insensitive to changes in prothrombin and Factor VII resulting from coumarin administration. Safe therapeutic levels with the use of that thromboplastin should have been held between 18 and 25 seconds instead of the 25 to 39 seconds' range usually recommended here. As a result the doctors in charge of the cases were maintaining these patients at excessively high levels (Figs. 5 and 6) not apparent from the reported prothrombin times. The evidence suggests that this may have been significant in causing the fetal deaths although the only pathological support we have that bleeding actually did cause death is the finding of hemoglobin-stained organs in Case 1 (Table IV). The macerated state of the fetuses may have prevented seeing more significant changes like those found by Sacks and Labate.<sup>21</sup>

Finally, a patient in the same group was delivered of an anomalous living infant with optic atrophy, microcephaly, and cerebral agenesis. In her case, treatment had been started in the twenty-fourth week of gestation and continued until term. As these anomalous organs were already formed by the twenty-fourth week,<sup>17, 18</sup> we do not feel that anticoagulants played a part in this tragedy.

Administration of high dosages of anticoagulants did not seem by itself of great danger to fetal survival as long as the therapeutic range was not exceeded. In the 3 patients on long-term therapy, all of whom required large amounts of drugs, no adverse fetal effects were noted. These patients received vitamin K<sub>1</sub> by mouth in small amounts whenever the prothrombin time became elevated above the desired level. Unfortunately, in the instances where fetal death occurred, no indication of overtreatment existed at the time either by reported prothrombin times or by evidence of hemorrhage. In retrospect, these patients were kept above the therapeutic range for prolonged periods.

*Comment:* In summary, we find in the 33 patients who were treated with anticoagulants ante partum 2 instances of intrauterine fetal death probably related to this treatment. In both of these cases inadvertant excessive depression of prothrombin concentration appears to be responsible. Our series

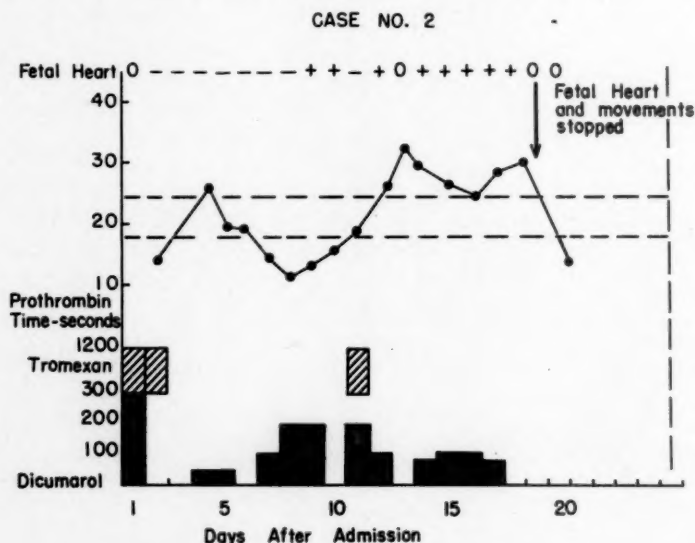


Fig. 6.

shows that the amount of drug administered is not so important as the effect measured by prothrombin time determinations in the mothers' blood. Consequently, the reliability of this determination as well as the corresponding correction in therapeutic range for each laboratory seems to be of the utmost importance in preventing such accidents.

*E. Postpartum therapy and recurrences:* Of 57 patients with antepartum thrombophlebitis, 19 were given anticoagulants in the postpartum period either prophylactically or as part of a treatment for the original episode. Among these 19 patients one postpartum hemorrhage occurred. This was discussed previously (Case 6, Table III). Two other instances of somewhat excessive bleeding were noted. In one the prothrombin time was below the ideal therapeutic range and treatment consisted of administration of vitamin K<sub>1</sub> only. The second was due to retained secundines and subsided without cessation of therapy. No excessive bleeding or hemorrhage occurred in the 38 patients in this series who did not receive anticoagulants, although such complications are not very rare.

As to recurrences, in the treated group one patient, one of the "clotters," developed an extensive superficial phlebitis. Therapy had been discontinued



for delivery and this episode occurred 12 hours after a first dose of Hedulin, before an effective therapeutic level had been reached. The untreated group showed 6 recurrences of superficial phlebitis mostly localized and one deep phlebitis. No pulmonary emboli were noted in either group.

*Comment:* The treatment of thrombophlebitis and indications for prophylactic anticoagulation, post partum, will not be discussed in this report. However, 8 recurrences were noted in this survey among 57 patients in the postpartum period that followed a pregnancy complicated by phlebitis, while only one occurred in the 19 who received anticoagulants at the time. The high incidence of recurrent thrombophlebitis in the postpartum period indicates that prophylactic anticoagulation is advisable in this situation.

*F. Delivery under anticoagulant therapy:* In this series 2 patients were delivered under full anticoagulant therapy. The first instance occurred intentionally because of a recent severe pulmonary embolism (Case 4, Table I). The prothrombin time on the day of delivery was 31.2 second (control 17.4). No excessive blood loss occurred despite a first-degree laceration. The infant was normal. At birth he was given 4 mg. of vitamin K<sub>1</sub> intramuscularly and had no subsequent difficulty. In the second instance vitamin K<sub>1</sub> was given to the mother during labor in sufficient amount to inactivate the anticoagulant effect. Delivery occurred too soon for this therapy to be effective, however, and somewhat excessive bleeding from an episiotomy was noted but the estimated total blood loss amounted to only 300 c.c. The infant was normal.

One patient under long-term therapy for recurrent thrombophlebitis was taken off anticoagulants 2 weeks prior to the expected date of delivery. Three days later phlebitis recurred, complicated by a pulmonary embolism (Case 5, Table II); Tromexan was then started again. This patient as well as the 2 others on long-term therapy had a normal prothrombin time on the day of delivery because of either resistance to anticoagulants or administration of vitamin K<sub>1</sub> at the onset of labor. All the infants were delivered spontaneously. Only one was given vitamin K at birth. This was an excessive-sized, anomalous infant who showed a subconjunctival hemorrhage. Seventeen days later she presented symptoms and signs of intracranial hemorrhage which probably was not related to anticoagulants since she had received vitamin K in sufficient amounts previously to annul prothrombin deficits. No abnormal bleeding occurred in the mothers.

*Comment:* Our experience with delivery under the effect of coumarin derivatives is rather limited. Adamson, Weaver, and Jaimet<sup>1</sup> in their series reported 2 cases in which full anticoagulation was carried on throughout parturition. They also noted no complications. At this time, however, there does not appear to be sufficient experience with this particular method to warrant its use, and some reports indicate it might be dangerous.<sup>19, 22, 27</sup> In evaluation of such therapy two important considerations must be kept in mind; its influence, first, on the inherent complications of labor and delivery, i.e., premature separation of the placenta, postpartum hemorrhage, etc., and, second, on the clotting ability of the infant's blood, i.e., hemorrhagic disease, traumatic delivery, etc.

Three less dangerous solutions to these problems can be suggested:

1. Stopping treatment one or 2 weeks prior to delivery in patients on long-term treatment or in those in whom the phlebotic process is not recent. This solution, however, may predispose to thromboembolic recurrences near term and does not take into account the fact that phlebotic episodes do occur in that period which would be benefited by anticoagulant therapy.

2. Carrying the patient at prothrombin levels below the therapeutic range (20 to 25 seconds for example) in the last days prior to delivery and through

labor. Another variant would be to carry the patient in the normal therapeutic range and give vitamin K<sub>1</sub> to the mother at the onset of labor. Full effect from this therapy could be expected 8 to 12 hours later at the most. By this time, however, many primigravidas and a majority of multiparas would be delivered. Protection from hemorrhagic complications of the mother and infant during labor and delivery would seem then to be better attained by the use of the subtherapeutic approach and administration of vitamin K<sub>1</sub>. Whatever technique is followed, it is advisable to give vitamin K<sub>1</sub> to the newborn in small amounts (1-2 mg. per baby intramuscularly).

3. Finally, stopping coumarin therapy prior to the onset of labor and using heparin thereafter until parturition begins. Protamine sulfate could then stop treatment immediately. We have had no experience with this therapeutic plan but theoretically the large molecular size of heparin might protect the infant as mentioned previously. Experimental and clinical work is necessary before this method can be evaluated.

In the past experience of this clinic the use of coumarin derivatives within a suboptimal therapeutic range and vitamin K<sub>1</sub> administration at the onset of labor appears to be a safe approach to anticoagulant therapy during parturition and delivery. In employing any of the discussed plans, an approximate time when labor seems imminent must be fixed. It is well known that this cannot be done successfully in all instances. For practical application, however, the state of the cervix on vaginal examination as regards softening, effacement, and dilation may be used with fair accuracy. In the presence of a "ripe" cervix these important shifts in therapy should be made.

There appears to be no contraindication to the use of elective induction of labor in a patient who has no evidence of active thrombophlebitis and who has been ambulatory, provided all ideal criteria for this procedure are completely satisfied. By this technique, a day when the prothrombin time is at the desired level could be selected, minimizing the risk of hemorrhagic accidents.

### Summary and Conclusion

The case histories of 57 patients who presented antepartum thrombophlebitis have been reviewed. General factors concerning the incidence of this disease are discussed. Since no significant comparison between patients under different types of therapy could be established, the conclusions of this survey are limited to the incidence of complications and suggestions as to anticoagulant therapy in the pregnant patient.

A total of 33 patients were treated in the antepartum period with coumarin derivatives; 4 more received anticoagulants only post partum. The high incidence of thromboembolic complications under conservative therapy, as well as under anticoagulants before effective prothrombin levels were attained justifies this latter form of treatment. Quick-acting anticoagulants should be used initially, however. Only one serious hemorrhagic complication occurred in the mother during anticoagulant therapy, a postpartum hemorrhage which may have been due to retained secundines.

Coumarin derivatives may have deleterious effects in pregnancy as evidenced by 2 instances of intrauterine death in this series apparently related to such therapy and confirming previous reports. These complications, however, were associated with excessive depression of coagulation in the mother. For this reason we recommend using heparin alone in the antepartum period

if the clinician is not sure of the reliability of the prothrombin determinations or if he is not skilled in the use of coumarin derivatives. On the other hand, should these prerequisites be filled, coumarin derivatives can be used with relative safety provided the prothrombin concentration of 15 per cent (prothrombin time of 35 seconds in this laboratory) is not exceeded. This can be achieved through the use of frequent prothrombin determinations and vitamin K<sub>1</sub> in small amounts by mouth whenever excessive anticoagulant effect occurs. After an episode of phlebitis anticoagulant therapy should be continued for a minimum of 2 weeks. In this clinic a treatment period of 6 weeks with a gradual decrease of dosage before cessation of therapy is the accepted practice. However, long-term anticoagulant therapy should be continued without hesitation in patients with repeated episodes of thrombophlebitis.

Delivery under anticoagulant treatment remains a problem not completely solved. A relatively safe approach is to keep the patient at a suboptimal therapeutic level of prothrombin time near delivery and administer vitamin K<sub>1</sub> at the onset of labor. In this situation vitamin K<sub>1</sub> should also be given to the newborn in small amounts. In view of the high incidence of thromboembolic recurrences which occur during the postpartum period, prophylaxis with anticoagulants seems indicated in patients who have suffered an episode of phlebitis ante partum.

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## DEPARTMENT OF CURRENT OPINION

### *Re-evaluation*

Dr. Catharine Macfarlane, the distinguished Research Professor of Gynecology at the Woman's Medical College in Philadelphia, has long been a vocal advocate of the routine pelvic examination for the well woman, and has contributed tremendously to our knowledge of the value of such a routine.

Reviewing her extensive writings over the past decades on this subject, one finds the following sentences, selected here to indicate the gist of her previous comments: "It would have been interesting to have made routine vaginal smears in connection with these periodic pelvic examinations" (1951). "This fifteen-year research has demonstrated the value of periodic examination of the female pelvic organs and breasts of presumably well women." "On the basis of this research, we conclude that the death rate from cancer of the uterine cervix could be materially reduced if all such women were given a pelvic examination at least once a year. We recommend that this be adopted as a minimum standard for good medical practice" (1955).

These, however, are selected sentences. Her present re-evaluation of the place of the cytologic smear as a routine part of pelvic examination should also be prefaced by these previous statements of hers: "If the supply of physicians were unlimited, if time and money meant nothing to the lay public, such examinations could be recommended without reserve for all women 30 years of age or over. In the world as it is today, a more realistic approach to the problem becomes necessary" (1955). And no re-evaluation could be introduced without quoting the opening sentence of a paper she wrote in 1935: "In a time of rapidly changing opinion, when the indivisible atom of our childhood has been split into many parts, when Newton's law no longer accounts for the falling apple and when the ovum no longer dominates menstruation, it becomes necessary to scrutinize carefully each familiar fact."



## VAGINAL CYTOLOGY—WHICH PATIENTS SHOULD HAVE PRIORITY?

### A Re-evaluation Based on 3,000 Office Patients

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**A**FTER thirty years, Dr. George Papanicolaou's discovery of the value of vaginal cytology in the detection of early cancer of the uterine cervix is receiving general recognition. Simultaneously there is general recognition of the fact that the number of technicians and pathologists qualified to interpret vaginal cytology is utterly inadequate. Until this test becomes more generally available, it will be necessary, in recommending it, to give priority to those women in whom cancer of the uterine cervix most frequently occurs.

To this end, and since the disease occurs very rarely in women under 30, I have reviewed the records of 3,000 office patients (white women, 30 to 77 years of age) with reference to the incidence of pelvic cancer. The value of the series is to some extent impaired by the fact that Jewish women (in whom cancer of the cervix rarely occurs) are included.

The series is divided into three groups. The first comprises 1,000 single white nulliparous women, 30 to 77 years of age. The second group comprises 1,000 married white nulliparous women, 32 to 65 years of age. The third group comprises 1,000 married white women, 35 to 73 years of age who have borne children. The findings are summarized in Tables I-III.

TABLE I. ONE THOUSAND SINGLE WHITE NULLIPAROUS WOMEN (30 TO 77 YEARS OF AGE)

CANCER SITE	NO.
Cervix	3
Body of the uterus	17
Ovary	2
Fallopian tube	0
Vagina	2
Vulva	0
Total	24

Since the chief value of the test lies in the detection of early cancer of the cervix, we are particularly interested in that lesion.

The first cancer of the cervix in this group occurred in a woman (M. T.) 47 years of age, menstruating regularly. She was referred on Feb. 26, 1941,

because of vaginal bleeding, practically continuous, for 6 months. Examination showed a papillary growth of the cervix, 2 by 3 cm. in diameter, which bled freely on touch. Biopsy showed squamous cell carcinoma. The uterus was small and movable. There was no evidence of broad ligament involvement.

The patient received 6,500 mg. hr. of radium followed by a series of x-ray treatments. Examination on Oct. 16, 1957, showed no evidence of cancer. This was a Stage I case, with a 16 year cure.

The second cancer of the cervix was in a 57-year-old woman (O. G.). She was 3 years past the menopause and was referred on Dec. 8, 1943, because of a blood-stained discharge of 6 months' duration. Examination showed a papillary growth, 0.5 by 2 cm. in diameter, projecting through the external os. A fragment of tissue showed squamous cell carcinoma. I never saw the patient again. Her physician died. Inquiry by mail revealed the fact that the patient died in 1945. Cause of death: "cancer of the uterus."

The third patient (M. S.) with cervical cancer was referred on Dec. 5, 1949. A diagnostic curettage and cervical biopsy were performed. The pathologist reported squamous cell carcinoma. She received radium, 6,090 mg. hr., and x-ray 10,000 r. Examination in January, 1958, showed the vagina obliterated by adhesions. There was no evidence of enlargement of the cervix or of broad ligament involvement. This is a 9 year cure.

TABLE II. ONE THOUSAND MARRIED WHITE NULLIPAROUS WOMEN (32 TO 65 YEARS OF AGE)

CANCER SITE	NO.
Cervix	5
Body of the uterus	6
Ovary	0
Fallopian tube	0
Vagina	0
Vulva	1
Total	12

The cancer of the vulva occurred in a 60-year-old woman (M. M.). She came complaining of "itching of privates, followed by a lump on the left which opened and discharged for 3 weeks." Vulvectomy and bilateral inguinal lymphadenectomy were performed on Feb. 7, 1956. The glands were not involved. She showed no signs of disease on Feb. 3, 1958.

TABLE III. ONE THOUSAND WHITE MARRIED PAROUS WOMEN (35 TO 73 YEARS OF AGE)

CANCER SITE	NO.
Cervix	10
Body of the uterus	8
Ovary	3
Fallopian tube	1
Vagina	0
Vulva	0
Total	22

A summary of the combined groups is shown in Table IV.

Our figures indicate that while cancer of the cervix can occur in single nulliparous women, it is extremely rare (3 cases per thousand). Dr. Fabian Gagnon of Quebec (*Laval médicale*, 1950) called attention to the low incidence of this form of cancer in nuns. Dr. Janet E. Towne of Loyola University, Chicago, reported 6 cases of cancer of the cervix in 13,000 celibate women (*Am. J. Obst. & Gynec.*, March, 1955).

TABLE IV. INCIDENCE OF PELVIC CANCER IN 3,000 WHITE WOMEN (30 TO 77 YEARS OF AGE)

CANCER SITE	1,000 SINGLE WHITE NULLIPAROUS	1,000 MARRIED WHITE NULLIPAROUS	1,000 MARRIED WHITE PAROUS
Cervix	3	5	10
Body of the uterus	17	6	8
Ovary	2	0	3
Fallopian tube	0	0	1
Vagina	2	0	0
Vulva	0	1	0
Total	24	12	22

Various theories may be advanced to account for the high incidence of cancer of the cervix in the married parous group (10 cases per 1,000). These include laceration of the cervix during childbirth, subsequent infection of these lacerations, a possible carcinogenic factor in smegma.

### Summary and Conclusions

The records of 3,000 office patients, 30 to 77 years of age, showed cancer of the uterine cervix to occur almost twice as often in married parous women as in married nulliparous women, and to occur more than 3 times as often in married parous women as in single nulliparous women.

A previous study showed cancer of the uterine cervix to be very rare in women under 30 years of age.

The small number of individuals qualified to interpret vaginal cytology make it imperative, for the present, to recommend these tests only for women in whom cancer of the cervix most frequently occurs, viz., in married women, 30 years of age and over, who have borne one or more children.

For the other groups, chief reliance must still be placed on periodic pelvic examination, including a careful inspection of the cervix.

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## RE-EVALUATION OF THE HUDGINS CANNULA

A. P. HUDGINS, M.D., CHARLESTON, W. VA.

THE AUTHOR<sup>1</sup> in 1945 presented the use of a screw type, retained cannula with a valve and detachable handle for uterosalpingography. Its original purpose was to make the x-ray study of the uterus and tubes an office procedure allowing the patient to be ambulatory.

It was originally proposed that the physician in his own office would pass a cervical sound and insert the screw type cannula and valve with clock-like rotation until it was held firmly within the cervix. After the handle is removed, a syringe and metal extension tip are attached, and the radiopaque material injected.

The cannula is retained, the handle and extension tip are removed, and the patient becomes ambulatory and may walk to the x-ray department. After about 20 minutes, the plate is taken. This allows spill from the tubes if patent.

The patient returns to the physician's office for removal of the cannula.

The film interpretation is based on the following principles: the uterus should be outlined; the normal tubes should contain no medium or show a very fine line; and the medium should be seen free in the peritoneal cavity in "splash form" or streaked. If the uterus is outlined and the tubes not outlined, there is obstruction of the tubes at the uterine end. If the medium is retained lateral to the uterus in a well-outlined elongated enclosure, the tubes are closed at the distal end.

The method has continued to prove itself to be a satisfactory procedure but, during its use for the past 15 years, certain observations have been made.

I. This cannula offers a method for prolonged, sustained, gentle intra-uterine pressure with the hope of opening the tube by a nonsurgical procedure. If tubal disease is found, the cannula may be allowed to be retained for 24 hours. Stimulated by the cannula and medium the uterus rhythmically contracts and exerts a gentle, safe pressure within the tubes which could overcome spasm of the tubes, expel a mucus plug, or free soft adhesions.

II. The introduction of the aqueous media\* which are radiopaque and are rapidly absorbed from the peritoneal cavity has necessitated a modification in technique.

The cannula is inserted firmly in the cervix as previously described. The handle is removed and a special retained metal extension tube is connected securely in the cannula with the other end extending out of the vagina. The posterior lip of the cervix is grasped by a special towel clamp. The special speculum is removed and the patient is ambulatory. Six cubic centimeters of

\*Salpix Contrast Medium, Ortho Pharmaceutical Corporation, Raritan, N. J.



aqueous opaque solution is injected at the x-ray department. The special instruments needed are the extension tip, towel clamp, and speculum. Before injection, the cannula should be tested by clocklike rotation of the extension to assure it is firmly within the cervix.

This has all of the advantages of simplicity, economy, and the ambulatory office technique with the advantage of the safe aqueous media. Usually a film of lesser density ("softer technique") is advised.

III. Many patients reported relief from menstrual cramps at subsequent menses after the insertion of the cannula for uterosalpingography. This is in keeping with the report of relief of dysmenorrhea from a regular cervical dilatation and curettage in about 60 per cent of the cases for about 6 months.

This result is accomplished, apparently, by the stretching of the cervix. The cannula can be inserted in the office and may be retained for several hours for mechanical stretching.

During these and other studies, the patients were questioned as to where pain was felt during cervical dilatation. In the majority of cases, about 83 per cent, it was referred anteriorly and low in the pelvis—"like a menstrual cramp." About 10 per cent of the patients complained of back pain—"like my menstrual backache," and 2 per cent of pain in the thighs. The other 5 per cent reported a combination of front and back pain or to the sides not well defined.

This prompted the trial of the cannula for ill-defined backache and pelvic pain without demonstrable abnormality, especially when associated with menses. When the cervical dilatation caused discomfort like the chief complaint associated with menstruation, that is, referred anteriorly or to the back, cervical dilatation with the cannula was considered possible therapy.

It is difficult to separate the psychic factors at times but favorable results have been temporarily obtained in correcting backache simply by inserting the cannula.

The retained cannula has also been effective in the treatment of obvious and occult cervical stenosis. The instrument is left in place for several hours.

#### Reference

1. Hudgins, A. P.: *AM. J. OBST. & GYNEC.* 49: 431, 1945.

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#### Erratum

In the article, "Mesonephroma of the Ovary," by Edmund R. Novak and J. Donald Woodruff, in the March, 1959, issue of the *JOURNAL*, in Table I, page 639, the age of Case 3 should have been given as a question mark instead of a seven.



## *Reviews and Abstracts*

EDITED BY LOUIS M. HELLMAN, M.D.

### REVIEWS OF NEW BOOKS

**Obstetrics and Gynecology.** By J. R. Willson, C. T. Beecham, I. Forman, and E. R. Carrington. 605 pages, 267 illustrations. St. Louis, 1958, The C. V. Mosby Company. \$10.75.

Members of the Department of Obstetrics and Gynecology at Temple University School of Medicine have collaborated under the direction of Dr. Willson to produce a worth-while, practical textbook. They state frankly that the text is derived from the expanded contents of course lectures offered to their medical students. The book does not delve deeply into theory nor does it dwell on details of management. References to controversial issues and experimental work are largely omitted. Conditions requiring consultation are indicated but the details of procedures requiring specialized training and experience (forceps, cesarean section, breech extraction, hysterectomy, etc.) are not included. The book will not provide all the information necessary for the physician to manage serious and complicated problems, but it will provide guideposts to aid him in recognizing a dangerous situation and it will indicate when consultation is needed.

There are isolated areas in this book with which the experienced obstetrician and gynecologist with fixed ideas may disagree but it does present a logical and conservative approach. The sequence of presentation of the subject material is especially attractive. The text proceeds from menstruation and its disorders through endocrine imbalances, infertility, pregnancy, and delivery to gynecologic disorders. Not quite so logically placed at the end of the book are isolated chapters on pediatric gynecology, clinical use of sex hormones, and gynecologic operations.

If the student knew all that is contained between the covers here he could pass any reasonable examination in both obstetrics and gynecology. If this be our aim then Willson and associates have done a good job. If, however, we aspire to scholarship and an inspiration to learning and, above all, education, neither this nor perhaps any other one-volume work will fill the bill.

**The Endocrinology of Reproduction.** Edited by Joseph Thomas Velardo. 340 pages, 191 figures, 18 tables, 1 plate. New York, 1958, Oxford University Press. \$15.00.

*Endocrinology of Reproduction* is composed of 340 pages and printed with smaller type than is usual in most medical books. This allows for more material without increasing the size of the book but makes reading more difficult. There are 9 contributors to the work and each one is a recognized authority on the topic discussed.

The book deals first with the genetics, then discusses the embryology of reproduction. The pregnancy hormones involved are discussed in detail and the pituitary and hypothalamus are completely covered. The discussion of the pituitary is the most complete I have seen. This chapter is most informative and contains all of the recent concepts concerning the anatomy and function of the pituitary.

The female and male reproductive systems are treated in separate sections. Each is discussed in great detail. Both sections contain modern concepts.

The effect of aging on reproduction occupies the final chapter, which is not long but of great significance.

Each section has a most extensive bibliography for those who wish to pursue specific items further.

**Schmerzlose Geburt durch Psychoprophylaxe.** By Dr. Fritz Roth. 124 pages, 8 figures. Stuttgart, 1959, Georg Thieme Verlag. \$2.85.

Psychoprophylactic preparation for painless childbirth, which was first developed by Nikolaiev in Russia and brought to France by Lamaze, is described. The method of Lamaze and the lectures from the "clinique des metallurgistes" in Paris are outlined and slightly modified. The psychoprophylactic preparation is based on Pavlov's concept of pain perception and on his theory of conditioned reflexes. The interpretation of the word "painless" by the author is important. He cites that 70 per cent to 80 per cent of the patients trained by his method do not have pains. This is somewhat misleading. It is known that the percentage of completely painless childbirth lies somewhere between 10 per cent and 20 per cent (Swiss clinics such as Geneva, Lausanne, and others). "Seventy to 80 per cent" refers to the patients who, during labor, had shown slight subjective symptoms of pain which were easily controllable.

The theory of "painless" childbirth is discussed and nine practical and theoretical lessons for the pregnant woman are given in detail. A comparison with the method of Read, better known in Anglo-Saxon countries, is made and it is the belief of the author that the psychoprophylactic method gives better results. The main difference lies in the fact that in the latter method the patient is exhorted to a great psychic and physical activity during labor. Unfortunately, the author does not discuss his own experience at the University Clinic of Berne and there is no real critical evaluation of the method. It is merely a translated "Leitfaden" from French into German of the original work of Lamaze and Veliay and others.

**Die pranatalen Infektionen des Menschen.** By Dr. Heinz Flamm. 136 pages, 4 tables, 2 figures. Stuttgart, 1959, Georg Thieme Verlag. \$4.70.

A good survey on the subject of antenatal infections of the human fetus is presented in the booklet of H. Flamm, of the Hygienic Institute of the University of Vienna, Austria. This is based on personal experience in the Vienna clinics and on the vast literature available. The author describes the viral infections as the most important. (There are special chapters on rubella and poliomyelitis in pregnancy.) Other chapters deal with the effect of vaccinations, infections such as herpes, Coxsackie, encephalitis, and the description of the cytomegalic inclusion disease as a "modern" virus entity. Other virus diseases like hepatitis epidemica, parotitis, psittacosis, Q fever, etc., are briefly discussed. The author emphasizes the importance of searching for viral infections in mothers who are delivered of children with malformations. Another part of the book gives short views on bacterial and fungus infections and infections with animal parasites like toxoplasmosis. Even the prenatal infection caused by some kinds of worms, a very rare condition in human pathology, is mentioned.

In a final chapter immunologic problems of the antenatal and neonatal periods are discussed. The author gives a short explanation as to why he prefers active immunization of the fetus in the neonatal period rather than a passive one by the vaccination of the pregnant mother.

A very extensive literature index, which constitutes one fourth of the book, gives excellent up-to-date references.

**Empfängnisverhütung.** By Heinrich Gesenius. 224 pages, 55 figures, 2 color plates. Munich and Berlin, 1959, Urban & Schwarzenberg. DM 28.

Professor Heinrich Gesenius of Berlin is no newcomer to the field of contraception. Several years ago, he contributed the chapter on "Empfängnisverhütung" in the highly respected handbook, *Biologie und Pathologie des Weibes*. An up-to-date and greatly expanded version of this chapter is now available in book form. Its publication is in itself a major milestone. No book on contraception has been written by a German scholar and published in Germany since 1932 when Ludwig Fraenkel's report appeared under the same title as that of Gesenius.

During the intervening period, birth control was under a heavy cloud in Germany and was the subject of repressive legislation which even today has not been repealed fully in some of the states of the Federal Republic. Most of the older physicians formerly identified with the birth control movement are dead or have left Germany. The younger generation of doctors have either received inadequate instruction or have had no training at all on the subject. In Germany, the great battle for a place for contraception within the framework of preventive medicine—a battle already fought and won so far as most American physicians are concerned—has not yet been joined. This is the background of Gesenius' book.

The volume covers many subjects beyond the confines of contraceptive techniques. It might even be argued that the wealth of information and lively personalized presentation of this book may confuse rather than enlighten readers seeking the clear-cut, simple manual of instruction so urgently needed in Germany at this time. Much space is given to the legal, religious, ethical, demographic, and eugenic aspects of birth control. This includes a discussion and refutation of claims of fetal damage caused by chemical contraceptives. Since the prospect of reducing the incidence of criminal abortion is a major argument among those advocating wider use of contraception in Germany, a long appendix of the book is devoted to this subject, and another, to infanticide. It may be questioned whether inclusion of photographs of decomposing cadavers, dismembered torsos, and other "horror pictures" is appropriate in a volume primarily intended for physicians.

In his use of statistics, Gesenius at times displays an amazing lack of critique. Whatever may have been the basis for the series of figures shown at the top of page 142, it should be obvious to any physician that an "expectation to conceive and give birth to a child" in only 65 of 100 nulliparous women, 20 years of age, cannot possibly reflect their reproductive capacity, as implied by the context. Moreover, another citation on the same page reveals that of 100 women, married at the age of 20 years, only 12.2 per cent were childless 5 years later.

The comprehensive bibliography (21 pages) will be particularly useful to those interested in German medical literature but foreign coverage leaves much to be desired both as to completeness and accuracy. American readers will find frustrating the German practice of citing from books without giving page references.

These shortcomings notwithstanding, it does great credit to Heinrich Gesenius that with his thoughtful and lively discussion he has broken a longstanding taboo against speaking on the subject of contraception and placed it once more in the public arena. This courageous step may well mark the opening of a new chapter in German gynecology.

**Year Book of Cancer, 1957-1958 Series.** Edited by Randolph Lee Clark, Jr., and Russell W. Cumley. 523 pages, 35 tables. Chicago, 1958, Year Book Publishers, Inc. \$8.00.

An attempt is made to review the more important publications pertaining to cancer in all the clinical fields. To the specialist well informed in any field, the restricted choice of articles will naturally leave much to be desired. However, the obstetrician and gynecologist will find reading this book a relatively painless and interesting way to keep up



with progress in the knowledge of cancer in allied fields. Especially pertinent is the section on breast carcinoma with reviews of the effects of oophorectomy, radiation of ovaries, adrenalectomy, and hypophysectomy.

The sections on pathology, cytology, radiation therapy, and cancer chemotherapy will naturally attract the gynecologist. Of special interest are the reviews of the genetic effects of radiation and of progress in the general methods of radiotherapy. The discouraging reviews on the clinical application of chemotherapy are of general interest, but the pathology and cytology section seems directed specifically to the general pathologist.

The basic science portion is divided into sections on epidemiology (excellent appraisal of lung cancer and general trends in cancer), biochemistry (purine metabolism, DNA studies, and enzyme systems), virology, and animal tumors. These sections, although necessarily restricted to the more important articles, are of extreme interest and are vital to the clinician interested in cancer. The impressions of Dr. Michael Shimkin, of the National Cancer Institute, on oncology in the Soviet Union are a sobering, worthwhile addition to the book.

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### BOOKS RECEIVED FOR REVIEW

- Amino Acids and Peptides With Antimetabolic Activity.** By G. E. W. Wolstenholme and C. M. O'Connor. 286 pages, 28 illustrations. Boston, 1958, Little, Brown & Company. \$8.75.
- Birth of Normal Babies.** By Lyon P. Strean. 194 pages. New York, 1958, Twayne Publishers, Inc. \$3.95.
- Cancer, Research into Causation, Volume 1.** By R. W. Raven. 558 pages, 116 tables, 94 figures. London, 1957, Butterworth & Co., Ltd. \$18.00.
- Cancer, Pathology of Malignant Tumors, Volume 2.** By R. W. Raven. 666 pages, 33 tables, 357 figures. London, 1958, Butterworth & Co., Ltd. \$18.00.
- Cancer, Volume 3.** By R. W. Raven. 501 pages, 82 tables, 165 figures. London, 1958, Butterworth & Co., Ltd. \$18.00.
- Cancer, Clinical Aspects, Volume 4.** By R. W. Raven. 555 pages, 173 figures. London, 1958, Butterworth & Co., Ltd. \$18.00.
- Convulsive Disorders of Children.** By Dora Hsi-Chih Chao, Ralph Druckman, and Peter Kellaway. 151 pages, 25 figures. Philadelphia, 1958, W. B. Saunders Company. \$6.00.
- Current Therapy—1959.** Edited by Howard F. Conn. 780 pages, 13 tables. Philadelphia, 1959, W. B. Saunders Company.
- Gynecologic Radiography (Including Radiography of the Breast).** By Jean Dalsace and J. Garcia-Calderon. 188 pages, 360 radiographs, 2 tables. New York, 1959, Paul B. Hoeber, Inc. \$8.00.
- Handbook of Medical Hypnosis.** By Gordon Ambrose and George Newbold. Second edition. 276 pages. Baltimore, 1958, Williams & Wilkins Company. \$6.75.
- Having a Baby.** By J. F. Robinson. Second edition. 100 pages, 23 figures. Baltimore, 1958, Williams & Wilkins Co. \$2.50.
- Heredity Counseling.** By Helen G. Hammons. 112 pages, 1 figure, 4 tables. New York, 1959, Paul B. Hoeber, Inc. \$4.00.
- Neo-Natal Paediatrics.** By W. R. F. Collis. 301 pages, 35 figures, 6 tables. New York, 1958, Grune & Stratton, Inc. \$5.00.
- Population: An International Dilemma.** By Frederick Osborn. 97 pages, 1 chart. Princeton, 1958, Princeton University Press.
- Urology in Outline.** By T. L. Chapman. 176 pages. Baltimore, 1959, Williams & Wilkins Company. \$6.75.



## *Items*

### **American Board of Obstetrics and Gynecology**

Applications for certification, new and reopened, for the 1960 Part I Examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. The deadline date for receipt of applications is Aug. 1, 1959. No applications can be accepted after that date.

Candidates for admission to the Examinations are required to submit, with their application, a plain typewritten list of all patients admitted to the hospitals where they practice, during the year preceding their application or the year prior to their request for reopening of their application. This information should be submitted on 8½" by 11" paper and is to be attested to by the Record Librarian of the hospital or hospitals where the patients are admitted. Necessary detail to be contained in the list of admissions is outlined in the Bulletin and must be followed closely.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office.

ROBERT L. FAULKNER, M.D., SECRETARY  
2105 ADELBERT ROAD  
CLEVELAND 6, OHIO

### **Award for Work on Obstetrics or Gynecology**

The Central Association of Obstetricians and Gynecologists is offering an award of \$250 for outstanding investigative or clinical work in the field of obstetrics and/or gynecology. Any accredited physician, research worker, or medical student living within the geographic confines of the Central Association is eligible. Papers must be written expressly for this competition and must be original. The winning paper will be presented at the annual meeting, to be held September 24 to 26, 1959, at Chicago.

Manuscripts should be submitted to the Secretary in triplicate, accompanied by an abstract not to exceed 150 words. No author's identification shall be shown on any of the 3 copies, the only identification being a covering letter addressed to the Secretary.

Papers should be in the hands of the Secretary by June 25, 1959.

EDWIN J. DECOSTA, M.D., SECRETARY  
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### **"Ortho" Prize of Canadian Society for the Study of Fertility**

The Canadian Society for the Study of Fertility is happy to announce the 1958 "Ortho" prize has been awarded to Professor C. P. Leblond and Dr. Y. Clermont of the Department of Anatomy, McGill University, for their paper on "Differentiation and Renewal of Spermatogonia in the Monkey *Macacus Rhesus*."

Those interested in submitting a paper to the Society for the 1959 "Ortho" prize of \$500 must do so before June 1, 1959. Further details may be obtained through the office of the Secretary of the Society.

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